FORMULATION AND EVALUATION OF EMRB042 ORALLY DISINTEGRATING TABLETS

Dissertation Submitted to the

The Tamilnadu Dr. MGR Medical University, Chennai

In Partial fulfillment

For the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted

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*This is to certify that this dissertation thesis entitled "***FORMULATION AND EVALUATION OF EMRB042 ORALLY DISINTEGRATING TABLETS"** *is a bonafide genuine research work carried out by* ***Mr. Gaurav Shrikant Bhide (Reg. No. 26106302)*** *in Partial fulfillment of the requirements for the award of degree in* ***Master of Pharmacy in Pharmaceutics,*** *of* ***The Tamilnadu Dr. M.G.R. Medical University, Chennai****, in the Research and Development Centre,* ***EMCURE Pharmaceuticals Ltd, pune,*** *under my guidance and supervision to my fullest satisfaction.*

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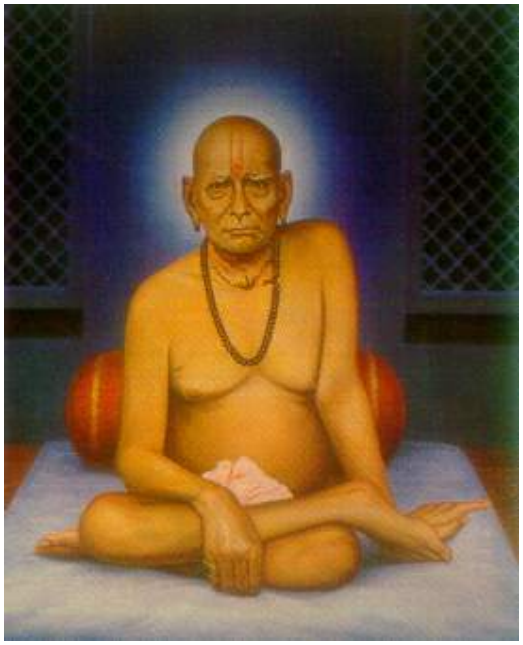
Dedicated to Almighty God

Shree Swami Samarth



&

My Beloved mother & sister

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9 CONCLUSION

In the present study attempts were made to formulate 150mg immediate release oral disintegrating tablet formulation which can provide effective and fast drug release in oral cavity.

EMRB042 oral disintegrating tablets were prepared by direct compression method. In vitro study showed formulation F10 & F11 were well suited for O.D.T formulation.

From the results obtained, it can be concluded that formulation F10 & F11 has achieved the objective of faster drug release, patient convenience and cost effectiveness as direct compression technology is used against the lyophilization technology used by innovator.

1) The use of sodium Stearyl Fumarate instead of magnesium stearate provided better release pattern.

2) Ludiflash due to polyvinyl acetate content increased disintegration time & therefore alters the release of the A.P.I.

3) Peroxide content of the Crospovidone played an important role in controlling the impurity in the formulation.

4) Use of calcium silicate as co-disintegrant provided better D.T & dissolution.

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1 INTRODUCTION

1.1 Orally disintegrating dosage forms

Orally disintegrating tablets (ODTs) are distinguished from conventional, sublingual tablets, buccal tablets and lozenges, which require more than a minute to dissolve in oral cavity. In the literature, ODTs also are called orodispersible, mouth dissolving, quick dissolve, fast melt and freeze dried wafers.

A quick dissolving tablet (also known as a fast dissolving, fast dissolving multi particulate, rapid dissolving, mouth dissolving, fast melting, or orodispersible tablets) is an oral tablet that does not require water for swallowing. The tablet dissolves within 60 seconds when placed in the mouth. The active ingredients are absorbed through mucous membranes in the mouth and gastrointestinal tract (GIT) and enter the blood stream. A fraction of pregastric drug absorption may bypass the digestive system and metabolism by the stomach acids and enzymes. In general, the tablets are physically robust and can be packaged in multi dose containers

A freeze dried wafer is a quick dissolving, thin matrix that contains a medicinal agent that does not need water for swallowing. This fragile dosage form requires unit dose packaging to ensure physical stability. The wafer disintegrates instantaneously in the oral cavity and releases drug, which dissolves in the saliva. The saliva is swallowed and the drug is absorbed across the GIT.Fast disintegrating or orodispersible tablets (ODTs) are one such novel approach to increase consumer acceptance by virtue of rapid disintegration, self administration without water or chewing. This delivery system offers convenience for treatment resistant population who has difficulty in swallowing unit oral dosage form, namely tablets and capsules. The demand for these formulations is particularly beneficial to pediatric and geriatric patients. It is estimated that 50 % of the population is affected by dysphagia which results in high incidence of noncompliance and ineffective therapy. To overcome this problem, it is necessary to design a formulation which rapidly disperse / dissolve in the oral cavity without the need of water for swallowing. Such dosage form should disintegrate when placed in the mouth and can be swallowed in the liquid form.

The major advantage of mouth dissolving tablets is high patient compliance and its disintegration in mouth; this could enhance the clinical effect of drug through pregastric absorption from mouth, pharynx and esophagus. In such a case bioavailability of a drug is significantly greater than those observed from conventional tablet dosage form by avoiding first pass metabolism. Moreover, they overcome the swallowing difficulty associated with geriatric, pediatric or psychiatric patients and for the conditions where patients may not have ready access to water thus, it provides convenience of administration, greater patient compliance and quick onset of action.

Due to the constraints of the current fast dissolving tablet (FDTs) technologies as highlighted above, there is an unmet need for improved manufacturing processes for FDTs that are mechanically strong, allowing ease of handling and packaging and with production costs similar to that of conventional tablets[1]

1.2 Need to formulate orodispersible tablets[1]

The need for non invasive drug delivery systems continues due to patient's poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses coupled with high cost of disease management. Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical companies. Pharmaceutical marketing is another reason for development of new dosage form because it allows a manufacturer to extend market exclusivity, while offering its patients population with a more improved and convenient dosage form.

The majority of patients receiving such preparations have little understanding of this new dosage form. Patients may be surprised when tablets begin to dissolve in the mouth. They might expect a faster onset of therapeutic action. Clarification from the pharmacist can avoid any confusion or misunderstanding[1].

1.3 Advantages of orodispersible tablets[2]

1. Improved patient compliance.
2. Rapid onset of action and may offer an improved bioavailability.
3. Patient having difficulty in swallowing tablet can easily administer this type of dosage form.

4. Useful for pediatric, geriatric and psychiatric patients.
5. Suitable during traveling where water is may not be available.
6. Gives accurate dosing as compared to liquids.
7. Good chemical stability.
8. Pregastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability.
9. An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets

1.4 Limitations

1. In case of bitter drugs the taste have to be masked by various techniques which in turn increases the time and cost of production.
2. Drugs to be absorbed at a particular site cannot be given in this dosage form.
3. Tablets are very fragile and lack physical resistance. Because the tablets are very porous and low compression forces are used to prepare them. Therefore they cannot be packed in conventional strips or in bottles. Special packaging is required.

1.5 Orodispersible tablets should have following properties[2]

1. They should disintegrate with the help of saliva within a matter of seconds.
2. They should be compatible with taste masking agent.
3. They should be portable without fragility concerns.
4. They should have a pleasing mouth feel.
5. They should leave minimal or no residue in mouth after oral administration.
6. They should exhibit low sensitivity to environment at conditions such as humidity and temperature.
7. They should allow manufacturer to use conventional processing and packaging equipments at low cost.
8. be adaptable and amenable to existing processing and packaging machinery

1.6 Mechanism for rapid disintegration[3]

To ensure that the tablet is fast dissolving, water must quickly egress into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet. Maximizing the porous structure of the tablet matrix and incorporating an appropriate disintegrating agents or highly water soluble excipients in the tablet formulation are the basic approaches used in current fast dissolving tablet technologies. Basically, the disintegrant's major function is to oppose the efficacy of the tablet binder and the physical forces that act under compression to form the tablet. The mechanism by which tablet is broken down into smaller particles and then produces a homogeneous suspension or solution is based on following mechanisms

1. Capillary action
2. High swellability of disintegrants
3. Capillary action and high swellability
4. Because of heat of wetting (Air expansion)
5. Due to particle repulsive forces
6. Due to deformation
7. Chemical reaction (Release of gases)
8. By enzymatic reaction

1.6.1 Capillary action

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipients and on tabletting conditions. For these types of disintegrants, maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

1.6.2 High Swellability

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling tablets with high porosity show poor disintegration due to lack of adequate swelling

force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

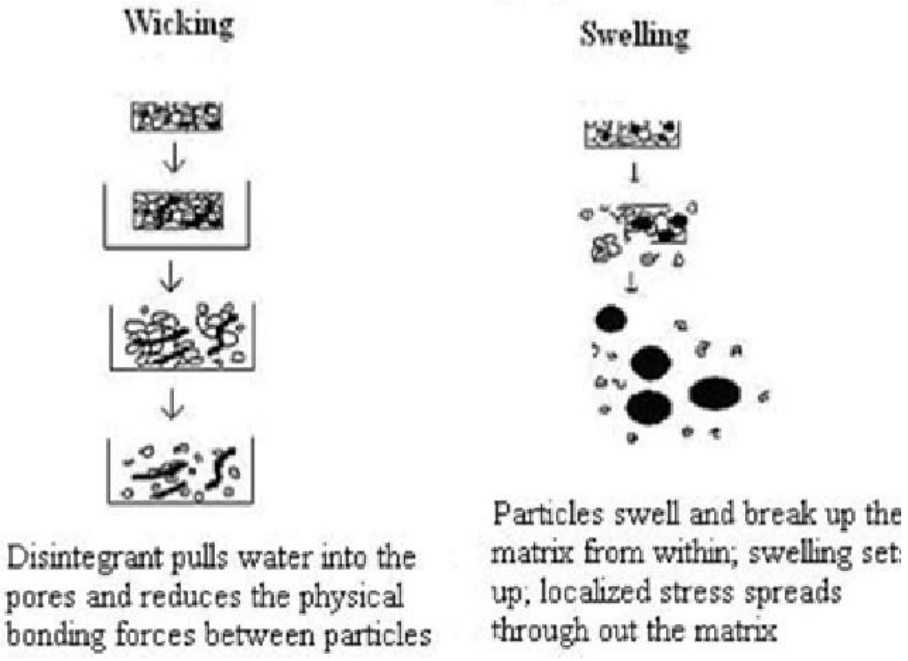


Figure No.1.1: Disintegration of tablet by wicking and swelling action.

1.6.3 Heat of wetting (Air expansion)

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

1.6.4 particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. The non swelling particle also causes disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

1.6.5 Deformation

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

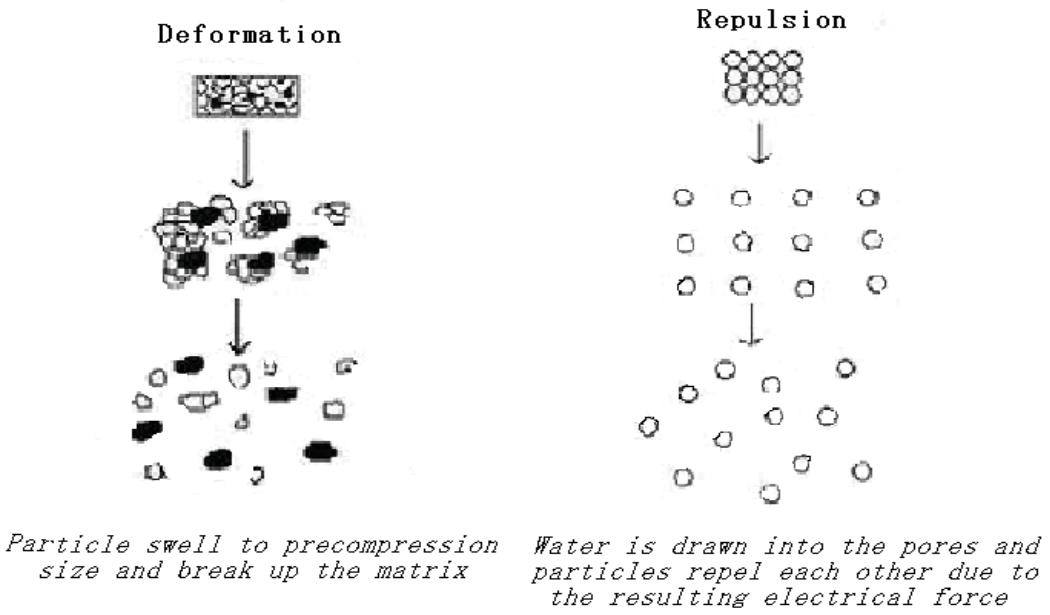


Figure No.1.2. Disintegration by Deformation and Repulsion.

1.6.6 Chemical reaction (Release of Gases)

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

1.6.7 Enzymatic reaction

Enzymes presents in the body also act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration. Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

1.7 Ingredients used for orodispersible tablets

1. They should allow quick release of the drug, resulting in faster dissolution and includes both the actives and the excipients.
2. The binder should maintain the integrity and stability of the tablet during compression.
3. The temperature of the excipient should be preferably around 30–35°C for faster melting properties.
4. The incorporation of binder should impart smooth texture and disintegration characteristics to the system.
5. Binders can either be liquid, semi solid, solid or mixtures of varying molecular weights such as polyethylene glycol. Commonly available fats such as cocoa butter and hydrogenated vegetable oils can also be used

1.8 Various technologies used in the preparation of orodispersible tablets [2]

1.8.1 Direct compression[4]

In this method, tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. Few drugs can be directly compressed into tablets of acceptable quality. A type of disintegrant and its proportion are of prime importance. The other factors to be considered are particle size distribution, contact angle, pore size distribution, tablet hardness and water absorption capacity. All these factors determine the disintegration. The disintegrant addition technology is cost effective and easy to implement at industrial level

1.8.2 Addition of disintegrant[5]

Microcrystalline cellulose, cross linked carboxymethyl cellulose sodium, cross linked polyvinyl pyrrolidone and partially substituted hydroxypropyl cellulose, though water insoluble, absorb water and swell due to capillary action and are considered as effective disintegrants in the preparation of first dissolving tablets. Fast disintegration of tablets can also be achieved by incorporating effervescent disintegrating agents, which generates carbon dioxide. This phenomenon also resulted in partial taste masking of unacceptable taste of the drug. The major drawback of effervescent excipients is their hygroscopicity (i.e., the ability to absorb atmospheric moisture). Hence, their manufacture requires control of humidity conditions and protection of the final product. This is reflected by the overall cost of the product.**(**Sharma et al)

Table No. 1. Various commercially available superdisintegrants along with their properties in brief

Sr no	Name	Type	Properties	Conc. Used (%)	Brand name
1.	Crospovidone	Polyvinyl-pyrroli-done	Rapidly disperses and swells in water.	0.5-5	Kollidon CL Polyplasdone XL
2	Micro crystalline cellulose	Micro crystalline cellulose	Breaking the hydrogen bonding between adjacent bundles of cellulose microcrystals.	10-20	Avicel
3.	Croscarmellose sodium	Modified cellulose	Excellent swelling and water wicking properties.	0.5-5	Ac-di-sol Primellose Solutab

Other super disintegrants which are rarely used are:

- Gellan Gum
- Xanthan Gum

1.8.3 Sugar based excipients[2]

Sugar based excipients are used for taste masking and as bulking agents. Most of the drugs are having unpleasant or bitter taste. The basic requirement for designing ODTs is that the drug should not have disagreeable taste so taste masking is necessary in most of the cases. Sorbitol, mannitol, xylitol, dextrose, fructose, isomalt, maltitol, polydextrose are mainly used. Aqueous solubility and sweetness impart a pleasing mouth feel and good taste masking. But not all sugar-based materials have fast dissolution rate and good compressibility or compactability. However technologies are developed to make use of the sugar based excipients in the design of fast dissolving tablets. Other ingredients commonly used are water soluble diluents, lubricants, antistatic agents, plasticizers, binders, colors and flavors. Sugar-based excipients are classified into two types on the basis of their moldabilty and dissolution rate. Type I Saccharides (e.g. lactose and mannitol) exhibit low moldability but high dissolution rate. Type II saccharides (e.g. maltose, maltitol) exhibit the high moldabilty but a low dissolution rate. Moldabilty in this respect defined as the capacity of the compound to be compressed. The moldability of Type I saccharides can be improved by granulating with it by type II Saccharides, This technology applied for rapidly disintegrating oral tablets that can effectively be manufactured by the crystalline transition of amorphous sucrose using the fluidized bed granulation method.

1.8.4 Spray drying[6]

A highly porous and fine powder is prepared by spray drying an aqueous composition containing support matrix and other components. This is then mixed with active ingredient and compressed into tablet

1.8.5 Sublimation[6]

The basis of this technique is to add inert solid ingredients that volatilize readily, e.g. camphor, ammonium bicarbonate, naphthalene, urea, urethane etc to other tablet excipients and the mixture is then compressed into tablets. Volatile material is then removed via sublimation, which generate a porous structure.

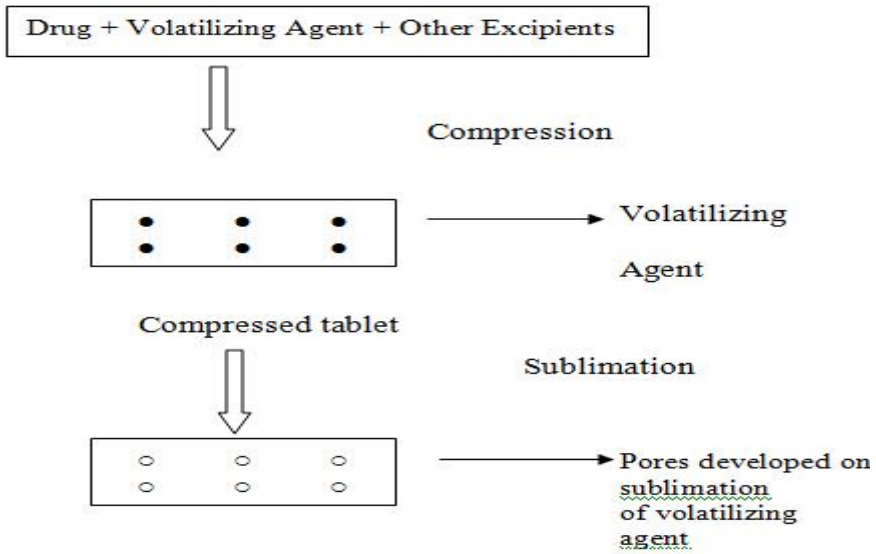


Figure No1.3 Steps involved in sublimation

1.8.6 Molding[2]

Tablets prepared by this method are solid dispersions. Physical form of drug in the tablets depends on extent it dissolves in the wetted mass. The drug can exist as discrete particles or micro particles in the matrix. It can dissolve totally to form a solid solution or dissolve partially in the molten carrier and remaining, if any, stays undisclosed and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel will depend on the type of dispersion. Different molding techniques can be used to prepare mouth dissolving tablets:

1.8.6.1 Compression molding

The powder mixture previously wetted with a solvent like ethanol/water is compressed into mould plates to form a wetted mass.

1.8.6.2 Heat molding

A molten matrix in which drug is dissolved or dispersed can be directly molded into orodispersible tablets.

1.8.6.3 Vacuum lyophilization

This process involves evaporation of solvent from a drug solution or suspensions at a standard pressure.

Molded tablets posses porous structure, which facilitates rapid disintegration and easy dissolution. Molded tablets offer improved taste due to water soluble sugars present in dispersion matrix. But molded tablets lack good mechanical strength and can undergo breakage or erosion during handling and opening of blister packs. However, adding sucrose, acacia or polyvinyl pyrrolidone can increase mechanical strength.

1.8.7 Freeze drying or lyophilization[7]

Lyophilization can be used to prepare tablets that have very porous open matrix network into which saliva rapidly moves to disintegrate lyophilized mass after it is placed in mouth. The drug is entrapped in a water soluble matrix which is freeze dried to produce a unit which rapidly disperses when placed in mouth. Apart from the matrix and active constituents, the final formulation may contain other excipients, which improve the process characteristics or enhance the quality of final product. These include suspending agents, wetting agents, preservatives, antioxidants, colors and flavors. The preferred drug characteristics for freeze drying formulations are water insoluble, low dose, chemically stable, small particle size and tasteless. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability.(US pat no.5,457,895)

1.8.8 Mass extrusion[8]

In this technique, a blend of active drug and other ingredients is softened using solvent mixture of water soluble polyethylene glycol, using methanol and then the softened mass is extruded through the extruder or syringe to get a cylinder of product, which is finally cut into even segments with the help of heated blades to get tablets. The dried cylinder can be used to coat the granules of bitter tasting drugs and thereby masking their bitter taste.

1.8.9 Nanonization

A recently developed Nano melt technology involves reduction in the particle size of drug to nano size by milling the drug using a proprietary wet milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into mouth dissolving tablets. This technique is especially advantageous for poorly water soluble drugs. Other advantages of this technology include fast

disintegration/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).

1.8.10 Taste masking[9]

Taste masking is an essential requirement for fast dissolving tablets for commercial success. Taste masking of the active ingredients can be achieved by various techniques:- microencapsulating into pH sensitive acrylic polymers, coating and fine granules of drug and disintegrant, coacervation using gelatin, using monoglycerides having a low melting point and by using ion exchange resin. Drug can be bound to the resin by either repeated exposure of the resin to the drug in a chromate graphic column or by prolonged contact of resin with the drug solution. Drugs are attached to the oppositely charged resin substrate, forming insoluble adsorbents or resonate through weak ionic bonding so that dissociation of the drug-resin complex does not occur under the salivary pH conditions.

Table No. 1. 2: Marketed fast dissolving tablets

Product	A.P.I	Manufacturer
Lamictal ODT	Lam199	GlaxoSmithKline
Felden fast melt	Piroxicam	Pfizer Inc., NY, USA
Zyprexia	Olanzapine	Eli Lilly, Indianapolis., USA
Pepcid RPD	Famotidine	Merck and Co., NJ, USA
Claritin Redi Tab	Loratidine	Schering Plough Corp., USA
Zoming-ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
Romilast	Montelukast	Ranbaxy Lab. Ltd., India
Olanex Instab	Olanzapine	Ranbaxy Lab. Ltd., India
Torrox MT	Rofecoxib	Torrent Pharmaceuticals., India
Nimulid MDT	Nimesulide	Panacea Biotech., India
Febrectol	Paracetamol	Prographarm, Chateauneuf, France

Zeplar TM	Selegilline	Amarin Corp., London, UKBristol
Tempra Quiclets	Acetaminophen	Bristol Myers Squibb, NY, USA

Table No1.3: Patented Technologies for Mouth dissolving tablets

Formulation	Key attributes	Company
Zydis®	Freeze-drying on blister packing	RP Scherer (Cardinal)
Lyoc	Freeze-drying on the shelves of freeze dryer	Laboratories L. Lafon, Maisons Alfort, France
Flashtab	Granulation of excipients by wet or dry granulation and compressing into tablets	Ethypharm France.
OraSolv	low compression force and an effervescent couple as a water-soluble disintegrating agent	Cima Labs Inc.
DuraSolv	Direct compression using water-soluble excipients	Cima Labs Inc.
WOWTAB®	High- and low-moldability saccharides	Yamanouchi Pharma
Pharmabrust	Direct compression of powder mixture	SPI Pharma
Advantol™ 200	Directly compressible excipient system	SPI Pharma
Advatab®	Direct compression using external lubrication system	Eurand
Microcaps	mask the bitter taste	Apatalis

Orally disintegrating formulations are required in diseases or disorders where the onset of action required is very fast like cardiac ischemia, hyper tension, head ache, tachycardia, bradycardia anti psychotic, anti depressants, migraine.

1.9 Migraine

The typical migraine headache is unilateral (affecting one half of the head) and pulsating in nature and lasting from two to 72 hours; symptoms include nausea, vomiting, photophobia (increased sensitivity to light) and phonophobia (increased sensitivity to sound) the symptoms are generally aggravated by routine activity. Approximately one-third of people who suffer from migraine headaches perceive an aura transient visual, sensory, language, or motor disturbances signaling the migraine will soon occur. Initial treatment is with analgesics for the headache, an antiemetic for the nausea, and the avoidance of triggers. The cause of migraine headache is unknown; the most supported theory is that it is related to hyper excitability of the cerebral cortex and/or abnormal control of pain neurons in the trigeminal nucleus of the brainstem. Propensity to migraine headache sometimes disappears during pregnancy, but in some women, migraines may become more frequent. Preventive migraine drugs are considered effective if they reduce the frequency or severity of migraine attacks by at least 50%.The major problem with migraine preventive drugs, apart from their relative inefficacy, is that unpleasant side effects are common. So, preventive medication is limited to patients with frequent or severe headaches.

Many medicines are available to prevent or reduce frequency, duration and severity of migraine attacks. They may also prevent complications of migraine. Beta blockers, such as Propranolol, atenolol, and metoprolol; calcium channel blockers, such as amlodipine, flunarizine and verapamil; the anticonvulsants sodium valproate, divalproex, gabapentin and topiramate; and tricyclic antidepressants are some of the commonly used drugs.

Tricyclic antidepressants have been found to be more effective than SSRIs Tricyclic antidepressants have been long established as efficacious prophylactic treatments. These drugs, however, may give rise to undesirable side effects, such as insomnia, sedation or sexual dysfunction. There is no consistent evidence that SSRI antidepressants are effective for migraine prophylaxis. While amitryptiline (Elavil) is the only tricyclic to have received FDA approval for migraine treatment, other tricyclic antidepressants are believed to act similarly and are widely prescribed, often to find one with a profile of side effects that is acceptable to the patient In addition to tricyclic a, the antidepressant nefazodone may also be beneficial in the prophylaxis of migraines due to its antagonistic effects on the 5-HT2A] and 5-HT2C receptors It has a more

favorable side effect profile than amitriptyline, a tricyclic antidepressant commonly used for migraine prophylaxis. Antidepressants offer advantages for treating migraine patients with comorbid depression selective seretonine reuptake inhibitor (SSRIs) are not approved by the FDA for treatment of migraines, but have been found to be effective by some practitioners

1.10 EMRB042[10, 11, 12]

EMRB042 is a selective 5-hydroxytryptamine receptor subtype agonist indicated for the acute treatment of migraine attacks with or without aura in adults. EMRB042is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. EMRB042is an agonist for a vascular 5-hydroxytryptamine receptor subtype (probably a member of the 5-HT_{1D} family) having only a weak affinity for 5-HT_{1A}, 5-HT_{5A}, and 5-HT_7 receptors and no significant affinity or pharmacological activity at 5-HT_2, 5-HT_3 or 5-HT_4 receptor subtypes or at alpha1-, alpha2-, or beta-adrenergic, dopamine1,; dopamine2; muscarinic, or benzodiazepine receptors. This action in humans correlates with the relief of migraine headache. In addition to causing vasoconstriction, experimental data from animal studies show that EMRB042also activates 5-HT_1 receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels, which may also contribute to the antimigrainous effect of EMRB042in humans. It binds to 5-HT $_{IB/ID}$ receptors, resulting in cranial vessel vasocontriction, inhibition of neuropeptide release, and reduced transmission in trigeminal pain pathways. Completely absorbed after PO use; rate of absorption of Mxlt-MLT is somewhat slower. Peak plasma levels, 1-1.5 hr; Mxlt-MLT: 1.6-2.5 hr. Food has no effect on bioavailability, but will delay time to reach peak levels by an hr. t 1/2: 2-3 hr. Metabolized by MAO-A; most is excreted through the urine is a significant first-pass effect.

1.11 clinical applications[11]

Acute treatment of migraine attacks in adults with or without aura.

Contraindications: Use in children less than 18 years of age, as prophylactic therapy of migraine, or use in the management of hemiplegic or basilar migraine. Use in those with ischemic heart disease or vasospastic coronary artery disease, uncontrolled hypertension, within 24 hr of

treatment with another 5-HT $_1$ agonist or an ergotamine-containing or ergot-type medication (e.g., dihydroergotamine, methysergide). Use concurrently with MAO inhibitors or use of EMRB042within 2 weeks of discontinuing a MAO inhibitor. Strongly recommended the drug not be given in unrecognized coronary artery disease (CAD) predicted by the presence of risk factors, including hypertension, hypercholesterolemia, smoking, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or males over 40, unless a CV evaluation reveals the client is free from CAD or ischemic myocardial disease.

1.12 A.P.I dosage[11]

Orally disintegrating Tablets- 5mg, 10mg.

Adults: Single dose of 5 mg or 10 mg. Doses should be separated by at least 2 hr, with not more than 30 mg taken in any 24-hr period.

2 LITERATURE REVIEW

1) Josel S. et al.developed orodispersible tablet of promethazine theoclate by direct compression using superdisintegrant combinations and subliming materials. Aqueous solubility of Promethazine theoclate is poor and thus late onset of action is observed. Formulations were developed using superdisintegrants (crosspovidone, CP and sodium starch glycolate, SSG) and co-processed superdisintegrants (CP: SSG 3:1, CP:SSG 1:1, CP:SSG 1:3) in different concentrations. After examining the flow properties of the powder blends, it was subjected to tablet compression. Prepared tablets were evaluated for thickness, hardness, friability, disintegration time, wetting time, water absorption ratio, weight variation, percentage drug content, invitro disintegration time, uniformity of dispersion and invitro dissolution studies. formulation containing CP: SSG 3:1 at a concentration 5% was found to be promising and selected as the optimized formulation. A similar formulation was prepared by sublimation technique and compared with the optimized formulation. This comparative evaluation revealed that direct compression method is a better alternative to sublimation method. It was concluded that dissolution rate of Promethazine theoclate can be enhanced to a great extent by direct compression technique with the addition of novel co-processed superdisintegrants which give immediate relief from emesis.

2) Patel T. et al developed a formulation containing topiramate, it is an anti-epileptic drug used to treat partial onset seizures, or primary generalized tonicclonic seizures in children and adults. But it's bitter in taste, and there is a critical need which to mask the taste. Different types of ion exchange resins like Kyron T-104, Kyron T-114, Kyron T-134, Doshion P 542 were used to form complex with Topiramate. Ion exchange resin to drug ratio, effect of pH, effect of temperature, effect of resin soaking time, effect of stirring time on complex formation were optimized. Drug and resin complex was evaluated for swelling, particle size analysis and drug release from drug and resin complex. So developed taste masked drug become eligible to formulate mouth disintegrating dosage form which was not a good candidate for orodispersible formulation before.

3) Adel M et al developed glimepiride (1 mg) rapidly disintegrating tablets (RDT) by direct compression, and also, evaluated Pharmaburst as a newly introduced diluent for this type of

tablets, either alone or in combination with other well known tablet excipients. Another goal was to study the stability, as well as, the in vivo effects of selected formulations. Orange flavor was the most preferred flavor for the prepared rapidly disintegrating tablets containing Pharmaburst as a single diluents. Pharmaburst alone is sufficient to produce rapidly (orally) disintegrating tablets of glimepiride with good physical characteristics, better compactability and shorter invivo and invitro disintegration time. The prepared Glimepiride RDT were found to have faster onset of action than the conventional glimepiride tablets. Also, they were effective in lowering fasting blood glucose levels (FBG) in rabbits. glimepiride RDT containing Pharmaburst alone were found to be stable when subjected to accelerated stability conditions (40 °C / 75 % relative humidity) for at least 3 months. Packaging the prepared Glimepiride RDT in 40 CC high density polyethylene (HDPE) bottles with 2 grams silica gel desiccant canisters and rayon had provided sufficient protection for the tablets. The used packaging system is believed to be very practical and convenient for elderly diabetic patients. It is also assumed to be preferred by the manufacturers.

4) JAIN C et al developed fast dissolving tablets of valsartan using different superdisintegrants by direct compression method. FDTs were evaluated for physicochemical properties and in vitro dissolution. Effect of disintegrant on disintegration behaviour of tablet in artificial saliva, pH 5.8 was evaluated. Wetting time of formulations containing Crospovidone was least and tablets showed fastest disintegration. The drug release from FDTs increased with increasing concentration of superdisintegrants and was found to be highest with formulations containing Crospovidone. The release of valsartan from FDTs was found to follow non-Fickian diffusion kinetics.

5) Patil M. et al developed teast masked the intensely bitter taste of tramadol hydrochloride and developed a orally disintegrating tablets for achievement of quick onset of action of the drug. Eudragit E 100 was used as a taste masking agent. Mass extrusion was the technique used for preparing taste masked granules and tablet was prepared with using superdisintegrants like crosspovidone, croscarmellose sodium and sodium starch glycolate, and evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. The prepared batches of tablets were evaluated for hardness, weight variation, friability, drug content,

disintegration time and in-vitro dissolution profile and found satisfactory. Among the formulations containing Crosspovidone was least and tablets showed fastest disintegration. The drug release from orally disintegrating tablets increased with increasing concentration of superdisintegrants and was found to be highest with formulations containing Crosspovidone. Thus results conclusively demonstrated successful masking of taste and fastest disintegration of the formulated tablets in oral cavity.

6) Prajapati B et al formulated directly compressible orally disintegrating tablets of Cinnarizine with sufficient mechanical integrity, content uniformity, and acceptable palatability to assist patients of any age group for easy administration. Effect of varying concentrations of different superdisintegrants such as crosspovidone, croscarmellose sodium, and sodium starch glycolate on disintegration time was studied. The disintegration time of the optimized CP5 batch was 25 sec. Good correlation was observed between disintegration time and water absorption ratio (R) for each of three superdisintegrants at concentrations studied. Considering the 'R' values and disintegration time, crosspovidone was significantly superior compared to other two superdisintegrants tested. Release of drug was faster from formulations containing 6% crosspovidone (CP5) compared to the marketed conventional Cinnarizine tablet. Differential scanning calorimetric studies did not indicate any excipient incompatibility, either during mixing or after compression. It concluded that directly compressible orally disintegrating tablets of cinnarizine with lower friability, acceptable taste, and shorter disintegration times were obtained using crospovidone at optimized concentrations.

7) Kannuri R et al developed a orally disintegrating tablets of escitalopram oxalate. Escitalopram oxalate is a selective serotonin reuptake inhibitor. The aim was to formulate orally disintegrating tablets of escitalopram oxalate using different ratios of Superdisintegrants LHPC 21, Kyron and crosspovidone, while microcrystalline cellulose, mannitol, prosolv ODT used as fillers. Tablets were prepared by direct compression method. The tablets were evaluated for hardness, thickness, friability, and weight variation and disintegration time, dispersion times and % drug release studies were performed. Tablets containing Crosspovidone, Kyron as disintegrants and mannitol as filler showed the best results and were disintegrated rapidly within 20 sec and 100% drug release was observed in 5mins.

8) Himabindu S. et al developed and evaluated oral disintegrating tablets (ODT) of metoprolol tartrate using super disintegrants, sodium starch glycolate, cross carmellose sodium and cross povidone in various diluents. Formulations F1 to F12 were prepared with various super disintegrants by using mannitol as diluent. From these formulations tablets prepared with cross povidone showed good release profiles. Formulations F13 to F16 were prepared by using cross povidone as super disintegrant and spray dried lactose as diluent and formulations F17 to F20 were prepared by using cross povidone as super disintegrant and dibasic calcium phosphate as diluent. Based on disintigration time and in vitro drug release profile F14 was selected as optimized formulation. Formulating as an ODT resulted in rapid onset of action as the tablets disintegrate in less than a minute. Taste masking which is an important aspect of ODT formulation is achieved by using the sweetener aspartame. No chemical interaction between drug and excipients was confirmed by FTIR studies.

9) Kakade S et al formulated orally disintegrating tablets of sertraline to achieve a better dissolution rate and further improving the bioavailability of the drug. Orally disintegrating tablets prepared by direct compression and using super disintegrants like crospovidone, croscarmellose sodium and sodium starch glycolate designate, designated as three different groups of formulation (A, B and C) respectively were prepared and evaluated for the precompression parameters such as bulk density, compressibility, angle of repose etc. The prepared batches of tablets were evaluated for hardness, weight variation, friability, drug content, disintegration time and in-vitro dissolution profile and found satisfactory. Among the three groups, group (C) containing crospovidone emerged as the best formulation and showed maximum dissolution rate with 98.49% drug release in 15 min. All three groups of formulations released the drug at faster rates than that of marketed conventional tablets of sertraline.

10) Balasubramaniam J. et al conducted study to evaluate the effect of crospovidone, croscarmellose sodium, and sodium starch glycolate on the dissolution rates of poorly soluble drugs with varying aqueous solubility which showed crospovidone type B to provide the fastest rate of dissolution for poorly soluble drugs. The fact that tablet strength and disintegration times for the tablets containing each drug and all the superdisintegrant studies showed that tablet

hardness and disintegration did not influence dissolution. Crospovidone type B has unique chemistry, particle size, and particle morphology that result in high interfacial activity, which significantly aids dissolution.

11) Rangole U. et al formulated rapidly disintegrating tablets by direct compression technology using hydrochlorothiazide as a model drug. Fast disintegrating tablet of hydrochlorothiazide was formulated using different concentration (2%, 3%, 4% and 5%) of superdisintegrants like Croscarmellose sodium and Crospovidone. All the batches were prepared by direct compression method using the Cadmach Single punch tablet compression machine using 8 mm flat punch. Disintegration time and drug release were taken as the basis to optimize the rapidly disintegrating tablet. Prepared tablets were evaluated for thickness, hardness, friability, uniformity of weight, disintegration time, wetting time and dissolution study. Crospovidone in the concentration of 4 % gives fasted disintegration in 16 sec. and shows 100% drug release within 14 min. is selected as the optimized formulation. Optimized formulation was subjected to stability studies for thirty days which showed stability with regards to release pattern.

12) Paul Y et al developed oral dispersible tablets (ODTs) of zidovudine, an antiretroviral drug, using different superdisintegrants viz. Crospovidone (PPXL), Crosscarmellose sodium (Ac-di-sol) and sodium starch glycolate by direct compression method. The effects of disintegrants in different concentration on the release profile of zidovudine ODTs were studied. Developed ODTs were studied for their physicochemical properties and invitro drug release profile. The studied parameters were found to be satisfactory for all ODT formulations of zidovudine. Disintegration times of all formulations were found to be less than 60 seconds. Disintegration time decreased with increase in disintegrant concentration. ODTs prepared using Ac-di-sol 6% possessed least disintegration time, offered better dissolution profile than that of all the ODTs formulations developed in the present investigation and that of marketed conventional tablet formulation of zidovudine. Ac-di-sol when tried in concentration above 6% resulted in an increase in disintegration time instead of further decreasing it. Accelerated studies proved that the optimized formulation was stable even after 3 months.

13) Kinchi et al formulated orally disintegrating tablets of solbutamol sulphate using direct compression technology by employing directly compressible fillers such as mannitol and microcrystal cellulose, varying concentrations of super disintegrants as Ac-di-sol, primogel, and polyplasdone XL in 2%, 3%, 4%, 5%. Formulations were evaluated for hardness, weight variation, friability, drug content, disintegration time and in-vitro dissolution profile study. All the formulations showed the satisfactory i.e disintegration within one min and complete release in three min. A4 and A8 were prepared with concentration of ac-di-sol less than 5% showed 100% release within 2 mins and 3 mins respectively, while 100% drug release of marketed conventional tablets was achieved in 25 min. which was much higher for the orally disintegrating tablets.

14) Parikh R. et al developed ordispersible tablet of atenolol. Tablets containing atenolol camphor, kyron –T 314 and lactose were prepared by direct compression method. Camphor was sublimated by th*e* exposure of the tablet to vacuum. Tablets were evaluated for the hardness, thickness, friability, weight variation, drug content, weight uniformity, *w*ater absorption ratio, in vitro dispersion time, invitro disintegration time, invitro dissolution profile. In investigation 3^2 full factorial *design* was employed to investigate joint effect of two variables. Amount of camphor and kyron –T 314.The result of multiple lin*ea*r regression analysis revealed that, for obtaining the rapid disintegration tablet should be prepared using optimum concentration of the camphore, and higher concentration of the kyron-T 314. A response surface plot presented graphically to represent the effect of independent variables on disintegration time, and percentage friability.

15) Senthil k et al formulated the fast dissolving tablets of metprolol tartrate to achieve better bioavailability of the drug. These formulations were prepared with varying concentrations of the disintegrants 4%, 5%, 6% of such as Crospovidone (PPXL), Crosscarmellose sodium (Ac-di-sol) and pregelatinised starch, alone with directly compressible mannitol to enhance mouth feel. The prepared tablets were evaluated for hardness, thickness, friability, weight variation, drug content, weight uniformity, *w*ater absorption ratio in vitro dispersion time, invitro disintegration time, invitro dissolution profile. Among the nine formulations F9 was found to be satisfactory, which showed the maximum dissolution of 99.67% in 8 minutes.

3AIM AND OBJECTIVES

3.1 Need for orally disintegrating formulation system:-

EMRB042 is indicated for the acute treatment of migraine attacks with or without aura in adults. These conditions require a delivery system capable of delivering the drug rapidly for immediate relief. EMRB042 is rapidly and fully absorbed on oral administration but the absolute oral bioavailability is about 45% and T_{max} is achieved at about 1 to 1.5hrs with oral administration suggesting a need for a delivery system with rapid achievement of Tmax. Orodispersible formulation can be considered as a solution to the above mentioned problem.

Thus the primary objectives were

1) Preformulation studies
2) To select appropriate ingredients and disintegrant on dissolution rate of orodispersible formulation.
3) To Prepare Orodispersible tablets of EMRB042 using direct compression technique.
4) To evaluate and characterize the prepared formulations.
5) Stability studies of prepared formulation.

4 PLAN OF WORK

4.1 Selection and Procurement of Drug and Excipients:

4.2 Preformulation Studies

- Evaluation of marketed formulation.
- Drug interaction studies.
- Spectral Analysis of EMRB042.

4.3 Selection of appropriate ingredients and disintegrant for orodispersible formulation.

4.4 Formulation of Tablet

- Direct Compression Method
- Wet granulation method

4.5 Evaluation of Powder Blend

- Bulk Density
- Taped Density
- Carr's Index
- Hausner's Ratio
- Angle of Repose

4.6 Evaluation of Tablets

- Hardness
- Thickness
- Friability
- Weight Variation
- Uniformity of Content
- InVitro Disintegration Test
- InVitro Dissolution Test
- Assay of test product

4.7 Stability studies of prepared formulation.

- InVitro Dissolution Test

4.8 Comparison of the optimized formulation with conventional marketed tablet of EMRB042.

5 MATERIALS AND EQUIPMENTS

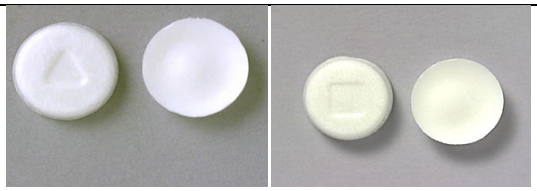
5.1 EQUIPMENTS

Table no.5.1 Equipments list

Sr. no.	Name of Equipment	Manufacturer
1	Rapid Mixer Granulator	Anchor mark Pvt. Ltd.
2	Rapid dryer	Retsch
3	Multi mill	Anchor mark Pvt.Ltd.
4	Moisture balance	Mettler Toledo
5	Double cone blender	SSPM Eng. System
6	Compression machine (16 station)	Cadmach
7	Friability tester	Electro lab
8	Hardness tester	Pharmg harness tester
9	Weighing Balance	Mettler Toledo
10	Tap density tester	Electrolab
11	Electromagnetic sieve shaker	Electrolab
12	Sieve	Electropharma
13	Malvern Mastersizer 2000	Malvern Mastersizer 2000

5.2 Innovator details

Table no.5.2 Innovator details

INNOVATOR DETAILS	
EMRB042 orally disintegrating Tablets	
Generic name	MXLT
Company	Merck & Co., Inc.
RLD	10 mg
Strength	5 / 10 mg
Label claim	Each Tablet contains EMRB042 10mg
Composition	Gelatin, Mannitol, Glycine ,Aspartame ,Peppermint flavor
Packing	Blister:- pealable blister having single tablets structure of blister
Thickness (mm)	10.0-11.5 mm (side-to-side)
Storage condition	Protect from excessive heat and humidity. Dispense in a tight container with child-resistant closure (as required).
Snaps	

5.3 Excipients

Table no.5.3 Excipients

Sr. No	name of Ingredient	Compendial Status	Trade name	Source	Use
1.	EMRB042	USP		Matrix	A.P.I
2.	Mannitol	USP	Pearlitol SD 200	Roquett-Pharma	Diluent
3.	Microcrystalline	USP	Avicel PH101	F.M.C-Bio polymer	Diluent
4.	Crospovidone	USP	Polyplasdone ultra	I.S.P	Binder
5	Calcium Silicate	USP	Hubersorb	J.M.Huber Corp	Anti caking agent
6	Croscarmellose Sodium	USP	Ac-di-sol	F.M.CBio polymer	Disintegrant
7	Ludiflash	USP	Ludiflash	B.A.S.F	Filler
8	Colloidal Silicon Dioxide	USP	Aerosil-200	evonik	Glidant
9	Aspartame	USP	-	Neutra weet	Sweetener
11	Sodium Stearyl Fumarate	USP	Pruv	J.R.S	Lubricant
12	Magnesium Stearate	USP	Veg grade	Merck	Lubricant

5.4 DRUG PROFILE[10,11,12]

EMRB042

5.4.1 Molecular weight- 391.4

5.4.2 Chemical Formula- $C_{15}H_{19}N_5$

5.4.3 Category- Antimigraine

5.4.4 Indications

EMRB042 is indicated to relieve acute migraine headaches (with or without aura).Headache, migraine

5.4.5 Organoleptic characteristics

Colour-White crystalline powder

Odour-odorless

Taste- bitter in taste

5.4.6 Mechanism of action

EMRB042's mechanism of action has not been established. It is thought that agonist activity at the 5-hydroxytryptamine (5-HT) $_{1B}$ and 5-HT $_{1D}$ receptor subtypes provides relief of headache. EMRB042 is a highly selective agonist at these receptor subtypes; it has no significant activity at 5-HT $_2$ or 5-HT $_3$ receptor subtypes or at adrenergic, dopaminergic, histamine, muscarinic, or benzodiazepine receptors. It has been proposed that constriction of cerebral vessels resulting from 5-HT $_{1B/1D}$ receptor stimulation reduces the pulsation that may be responsible for the pain of migraine headaches. It has also been proposed that EMRB042 may relieve migraine.

5.4.7 Absorption

Oral bioavailability is 45% Food has no effect on the bioavailability of EMRB042. However, administering EMRB042 with food will delay by 1 hour the time to reach peak plasma concentration. The rate of absorption is not affected by the presence of a migraine attack.

5.4.8 Protein binding

Low (14%)

5.4.9 Biotransformation

EMRB042 is metabolized by monoamine oxides A isoenzyme (MAO-A) to an inactive indole acetic acid metabolite. In addition, several other inactive metabolites are formed. An active metabolite, *N*-monodesmethyl-EMRB042, with pharmacological activity similar to that of the parent compound has been identified in small concentrations (14%) in the plasma.

5.4.10 Half life

Approximately 2 to 3 hours

5.4.11 Elimination

Approximately 82% and 12% of the dose was excreted in the urine and feces, respectively within 120 hours. Approximately 14% of EMRB042 was excreted in urine as unchanged and 51% as an indole acetic acid metabolite

5.4.12 Mutagencity

EMRB042 demonstrated no mutagenic or clastogenic effects in the microbial mutagenesis assay or in the invitro studies, including mammalian cell.

5.4.13 Fertility

A fertility study in female rats receiving oral doses of EMRB042 of up to 100 mg/kg per day approximately 225 times the AUC in humans receiving the maximum recommended human dose found changes in estrus cyclicity and delays in time to mating. The no effect dose was 10 mg/kg per day Also, a reproductive study in male rats receiving 250 mg/kg per day found no impairment.

5.4.14 Pregnancy

Trials have not been done in pregnant women. A reproductive study in female rats receiving doses of EMRB042 of up to 10 and 100 mg/kg per day prior to and during mating and throughout gestation and lactation found reduced birth weights and pre and post weaning weight gain in the offspring of the rats. Although there was no apparent maternal toxicity, developmental effects on offspring growth occurred. FDA Pregnancy Category is C.

5.4.15 Breast feeding

It is not known whether EMRB042 is distributed into human breast milk.

5.4.16 Geriatrics

Pharmacokinetic studies are not demonstrated. Geriatric specific problems that would limit the use of EMRB042 in geriatric patients older than 65 years of age, there was no difference in efficacy or overall side effects compared with younger adult.

5.2Excipients

5.2.1 Ludiflash

Ludiflash is composed of the following

90% Mannitol (Mannitol: EP, USP, JP)

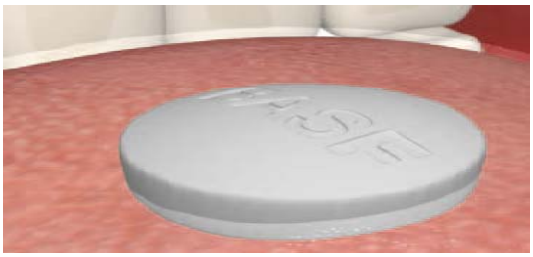
Fast dissolving filler with a mildly Sweet taste

5% Kollidon® CL-SF5 (Crospovidone) (Kollidon CL-SF: EP, USP, JPE)

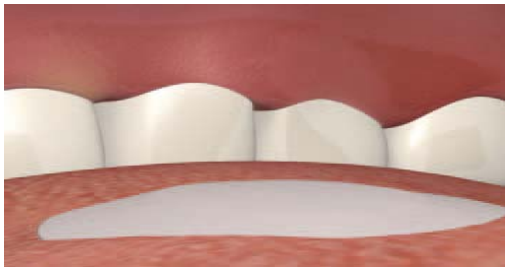
A superior tablet disintegrant Highly effective, disintegrates the tablet in the presence of very little liquid Offers a pleasantly smooth and Creamy mouth feel

5% Kollicoat (Kollicoat SR 30D: EP)

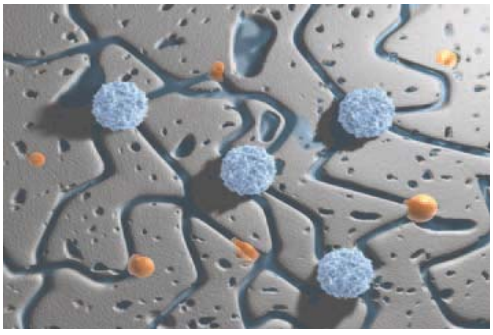
Hydrophobic binder for enhanced disintegration



With Ludiflash, a hard tablet disintegrates



It disintegrates completely to form a fine cream.



The highly porous tablet disintegrates very quickly

5.2.2 Microcrystalline cellulose[13, 14]

Synonyms	Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose
Functional Category.	Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant
Loss on drying	Not more than 7%
Density (true)	1.512–1.668 g/cm3
Solubility	Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.
Stability and Storage Conditions	Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place
Incompatibilities.	Microcrystalline cellulose is incompatible with strong oxidizing agents
Applications	Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tabletting

5.2.3 Croscarmellose sodium[15, 16]

Synonyms	Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum, Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.
Chemical Name	Cellulose, carboxymethyl ether, sodium salt
Functional Category	Tablet and capsule disintegrant.
Solubility	Insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.
Density	1.543 g/cm3
Stability and Storage Conditions	CCS is a stable though hygroscopic material.A model tablet formulation prepared by direct compression, with CCS as a disintegrant, showed no significant difference in drug dissolution after storage at 30°C for 14 months. CCS should be stored in a well-closed container in a cool, dry place.
Incompatibilities	The efficacy may be slightly reduced in tablet formulations by process that contain hygroscopic excipients such as sorbitol, CCS is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.
Applications	CCS is used as disintegrant for capsules,tablets, and granules. In tablet formulations, CCS may be used in both direct-compression and wet-granulation processes. In wet granulations, the CCS should be added in both wet and dry stages of the process for wicking and swelling .CCS at concentrations up to 5% w/w may be used as a tablet disintegrant.

5.2.4 Mannitol [17, 18]

Synonyms	Cordycepic acid; manna sugar;D-mannite; mannite; Mannogem; Pearlitol.
Chemical Name	D-Mannitol
Functional Category	Diluent; diluent for lyophilized preparations; sweetening agent; Tablet and capsule diluent; tonicity agent
Solubility	Alkalis Soluble Ethanol (95%) 1 in 83 Ether Practically insoluble Glycerin 1 in 18 Propan-2-ol 1 in 100 Water 1 in 5.5
Density	Density (true): 1.514 g/cm3
Stability and Storage Conditions	Stable in the dry state and in aqueous solutions. In solution, mannitol is not attacked by cold, dilute acids or alkalis, nor by atmospheric oxygen in the absence of catalysts. Does not undergo Millard reactions. The bulk material should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Mannitol solutions, 20% w/v or stronger, may be salted out by Potassium chloride or sodium chloride. Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic.
Applications	Used as a diluent (10–90% w/w) in tablet formulations, it is not hygroscopic and may thus beused with moisture-sensitive active ingredient, used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations. Granulations with mannitol have the advantage of being dried easily. Tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. As an excipient in the manufacturing of chewable tablet formulations because of its negative heat of solution, Sweetness, and 'mouth feel'

5.2.5 Crosspovidone[19, 20]

Synonyms	Crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.
Chemical Name	1-Ethenyl-2-pyrrolidinone homopolymer
Functional Category	Tablet disintegrant.
Solubility	Practically insoluble in water and most common Organic solvents.
Density	1.22 g/cm3
Stability and Storage Conditions	Since crospovidone is hygroscopic, it should be stored in an Airtight container in a cool, dry place
Incompatibilities	Crospovidone is compatible with most organic and inorganic Pharmaceutical ingredients. When exposed to a high water Level, crospovidone may form molecular adducts with some Materials
Applications	Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet and dry granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Particle size of strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Used as a solubility enhancer. With the technique of co-evaporation, Used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

5.2.6 Colloidal Silicon Dioxide[21, 22]

Synonyms	Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed Silica; light anhydrous silicic acid; silicic anhydride; silicon Dioxide fumed; Wacker HDK.
Chemical Name	Silica
Functional Category	Adsorbent; anticaking agent; emulsion stabilizer; glidant; Suspending agent; tablet disintegrant; thermal stabilizer; Viscosity-increasing agent
Solubility	Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.
Density	0.029–0.042 g/cm3
Stability and Storage Conditions	Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a ph 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a ph greater than 7.5 the viscosity-increasing properties of colloidal silicon dioxide are reduced; and at a ph greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates. Colloidal silicon dioxide powder should be stored In a well-closed container.
Incompatibilities	Incompatible with diethylstilbestrol preparations
Applications	Used in pharmaceuticals, cosmetics, and food products, Its small particle size and large specific surface area give it desirable flow characteristics That are exploited to improve the flow properties of dry powders in a number of processes such as tablet .Used to stabilize emulsions. And as a thixotropic thickening and suspending agent in gels and semisolid preparations. With other ingredients of similar Refractive index, transparent gels may be formed.

5.2.7 Sodium Stearyl Fumarate[23, 24]

Synonyms	Fumaric acid, octadecyl ester, sodium salt; Pruv; sodium Monostearyl Fumarate
Chemical Name	2-Butenedioic acid, monooctadecyl ester, sodium salt
Molecular Weight	390.5
Density	1.107 g/cm3
Functional Category	Tablet and capsule lubricant
Solubility	Acetone Practically insoluble Chloroform Practically insoluble Ethanol Practically insoluble Methanol Slightly soluble Water 1 in 20 000 at 258C 1 in 10 at 808C 1 in 5 at 908C
Stability and Storage Conditions	At ambient temperature, sodium stearyl fumarate is stable for Up to 3 years when stored in amber glass bottles with Polyethylene screw caps. The bulk material should be stored in a well-closed Container in a cool, dry place.
Incompatibilities	Sodium stearyl fumarate is reported to be incompatible with Chlorhexidine acetate.
Application	Sodium stearyl fumarate is used as a lubricant in capsule and Tablet formulations at 0.5–2.0% w/w concentration.(1–9) It is Also used in certain food applications

5.2.8 Magnesium Stearate[25, 26]

Synonyms	Dibasic magnesium stearate; magnesium distearate; magnesia stearas; magnesium octadecanoate; octadecanoic acid, magnesiumsalt; stearic acid, magnesium salt
Chemical Name	Octadecanoic acid magnesium salt
Molecular Weight	591.24
Density (true)	1.092 g/cm3
Loss on drying	Not more than 6%
Functional Category	Tablet and capsule lubricant
Solubility	Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).
Stability and Storage Conditions	Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.
Application	Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

Asparteme[27, 28]

Synonyms	3-Amino-N-(a-carboxyphenethyl)succinamic acid N-methylester; 3-aminoN(amethoxycarbonylphenethyl)succinamic acid; APM; aspartyl phenylamine methyl ester; Canderel; E951; Equal; methyl N-a-L-aspartyl-L-phenylalaninate; Nutra Sweet; Pal Sweet; Pal Sweet Diet;
Chemical Name	N-a-L-Aspartyl-L-phenylalanine 1-methyl ester
Molecular Weight	294.31
Density (true)	1.347 g/cm3
Loss on drying	<4.5%
Functional Category	Sweetening agent.
Solubility	slightly soluble in ethanol (95%); sparingly soluble in water. At 208C the solubility is 1% w/v at the isoelectric point (pH 5.2). Solubility increases at higher temperature and at more acidic pH, e.g., at pH 2 and 208C solubility is 10% w/v.
Stability and Storage Conditions	Aspartame degradation occurs during prolonged heat treatment; The bulk material should be stored in a well-closed container, in a cool, dry place.
Incompatibilities	Differential scanning calorimetry experiments with some directly compressible tablet excipients suggests that aspartame is incompatible with dibasic calcium phosphate and magnesium stearate. Reactions between aspartame and sugar alcohols are also known.
Application	Used as an intense sweetening agent in beverage products, food products, and table top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.

6 METHODOLOGY

6.1 Pre formulation studies

6.1.1 A.P.I characterization by X-ray diffraction method[29, 10]

6.1.1.1. Preparation of the sample

47 mg of EMRB042 are suspended in 35 ml of TBME (tetra-methyl-butyl-ether) and heated up to 35^0C then 0.2 ml of methanol is added at 60^0C to increase the solubility. The clear solution is then filtered through 0.22µm Millipore filtration unit. The filtered solution is then cooled to room temperature till clear solution seeded with 2mg of the ENRB042 form I. The obtained solution is further cooled to 5^0C and stored for 24 hours. The sample obtained was prepared in the disc shaped circular holder of 0.5 mm depth and 10mm width.

6.1.1.2 Evaluation parameters

X-ray powder diffraction measurement was performed on Philips 1710 powder X-ray diffractometer using cu $K\alpha_1$ =1.54060 Å. The x-ray source is operated at 45kV and 45mV spectra recorded at step size of 0.02^0 with continuing 2.4 seconds per step.

6.1.2 Organoleptic properties of the A.P.I.

Color: A small quantity of EMRB042 powder was taken in butter paper and viewed in well-illuminated place.

Taste and odor: Very less quantity of EMRB042 was used to get taste with the help of tongue as well as smelled to get the odor.

6.2 Physicochemical parameters of the A.P.I.

6.2.1 Bulk density of the A.P.I

A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit. Calculate the bulk density, in gm per ml, by the formula

Bulk density = Bulk Mass/ Bulk Volume

6.2.2 Taped density of the A.P.I

After observing the initial volume, the cylinder is mechanically tapped and volume readings are taken until little further volume changes observed. Cylinder dropping

distance: 14± 2 mm at a normal rate of 300 drops / minute. Unless otherwise specified, tap the cylinder 500 times initially and measure the tapped volume, VA. Repeat the tapping an additional 750 times and measure the tapped volume, VB. If the difference between the two volumes is less than 2%, then it is the final tapped volume that is Vf. Repeat the same for 1250 taps, as needed, if the difference between succeeding measurements is less than 2%. Calculate the tapped density, in gm per ml, by the formula

$$\text{Tapped Density} = \frac{m}{Vf}$$

6.2.3 Compressibility index of the A.P.I

The compressibility Index and Hausner's Ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free flowing powder, such interactions are generally less and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the compressibility Index and the Hausner's Ratio Calculated by the formula

$$\text{Compressibility index: } = 100\frac{(V_0 - Vf)}{V_0}$$

$$\text{Hausner's Ratio: } = \frac{V_0}{Vf}$$

6.2.4 Particle size analysis of A.P.I Malvern Mastersizer 2000

Method: Dry method

Procedure: Carefully assemble the flow cell and the lens into the main unit of the instrument. Connect small volume of dispersion cell to the main unit. Align the instrument after feeding the required parameters. Apply the pressure of 2 bar and feed rate of 50 % for proper cleaning of lenses. Measure the background. Add 1.0 gm of sample to the dry accessor and measure the sample by applying air pressure of 2 bar, feed rate of 50%. During the measurement laser obscuration should be between 2 to 6 %. Analyze the sample and report.

6.3 Compatibility Study by D.S.C technology and HPLC technology

Table no. 6.1 Drug-Excipients Compatibility Study

Sample name	Storage		
	40°C/75% RH 1 M open	40°C/75% RH 1 M closed	55°C 1 M open
EMRB042	Alone	Alone	Alone
EMRB042 + Mannitol	(1:1)	(1:1)	(1:1)
EMRB042 + Colloidal silicon dioxide	(1:1)	(1:1)	(1:1)
EMRB042 + Crospovidone	(1:1)	(1:1)	(1:1)
EMRB042 + Croscarmellose sodium	(1:1)	(1:1)	(1:1)
EMRB042 + Aspartame	(1:1)	(1:1)	(1:1)
EMRB042 + Peppermint flavor	(1:1)	(1:1)	(1:1)
EMRB042 + Sodium stearyl Fumarate	(1:1)	(1:1)	(1:1)
EMRB042 + Pharmaburst	(1:1)	(1:1)	(1:1)
EMRB042 + Ludiflash	(1:1)	(1:1)	(1:1)
EMRB042 + Prosolve ODT	(1:1)	(1:1)	(1:1)
EMRB042 + Prosolve ODT	(1:1)	(1:1)	(1:1)

EMRB042 was mixed with 1:1 proportion with all excipients to be used in our formulation and kept at 40°C/75% RH (close), 55°C (close), 55°C (open) for one month. The thermo grams & chromatograms obtained after month by D.S.C technology & HPLC technology studied to confirm the compatibility with the excipients

6.3.1 H.P.L.C technology[30]

The chromatographic column used was an Agilent ZorbaxSB-CN 250mm×4.6mm column with 5m particles. Mobile phase consists of a mixture of 10ml potassium di Hydrogen ortho phosphate, pH adjusted to 3.4 using diluted Orthophosphoric acid (solvent A), acetonitrile (solvent B) and Methanol (solvent C) the column temperature was maintained at 25^{o}C and the wavelength was monitored at a wavelength of 225 nm. The injection volume was 10µl for related substances determination and 5µl for

assay determination. Solvent A was used as diluent during the standard and test Samples preparation.

6.3.1.1 Preparation of standard solutions

A working solution of 500g/ml was prepared for related substances determination and assay determination analysis. A stock solution of Impurity (mixture of Imp-1, Imp-2 and Imp-3) at 500g/ml was also prepared in diluents.

6.3.2 D.S.C technology[31]

The D.S.C study was performed on (pure A.P.I) and (A.P.I + excipients). 2 mg of the sample was kept in heat sensitive sealed aluminum pans sample mixture was constantly heated at a rate of 10^{o}C/ min. in the range of 50^{o}C to 220^{o}C for 20 min. The nitrogen flow is controlled at the rate 20ml/min. Pressure of nitrogen was maintained constant at 2 τ (torr)**.** The themogram obtained is evaluated on basis of the melting point of the A.P.I.

6.4 Physicochemical parameters of powder blend.

6.4.1 Particle size analysis of powder blend by Sieving method

Procedure: This test was performed with the help of sieves of different size. They were fitted in the platform of sieve shaker in such a way that the coarse sieve was placed on top corresponding to the finer sieves. Placed 50 gm sample on the top and run the machine for 5 min. and took the weight of the retention on the sieve(s).Finally calculated the % of retention on each sieve by the following equation.

$$\% \text{ retained} = \frac{\text{quantity of retention}}{50} X\ 100$$

6.4.2 Flow properties of powder blend

Procedure: A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 10 gm of sample powder is filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, is found by measuring in different direction. The height of the heap was measured by using scale. The values of angle of repose are calculated by using the following formula

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} h/r$$

Where, h- height of the heap,

r- Radius of the heap

Angle of repose (Ø)	Flowability
< 20	Excellent
20-30	Good
30-34	Acceptable
> 40	Very poor

For most pharmaceutical powders, the angle of repose values range from 25 to 45, with lower values indicating better flow characteristics. Values of angle of repose ≤ 30 usually indicate a free flowing material and angle ≥40 suggest a poorly flowing material.

6.4.3 Bulk density of powder blend

Procedure: A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit. Calculate the bulk density, in gm per ml, by the formula

Bulk density = Bulk Mass/ Bulk Volume

6.4.4 Tapped density of powder blend

Procedure: After observing the initial volume, the cylinder is mechanically tapped and volume readings are taken until little further volume changes observed. Cylinder dropping distance: 14± 2 mm at a normal rate of 300 drops / minute. Unless otherwise specified, tap the cylinder 500 times initially and measure the tapped volume, VA. Repeat the tapping an additional 750 times and measure the tapped volume, VB. If the difference between the two volumes is less than 2%, VB is the final tapped volume, VF. Repeat the same for 1250 taps, as needed, unit the difference between succeeding measurements is less than 2%. Calculate the tapped density, in gm per ml, by the formula.

$$\text{Tapped Density} = \frac{m}{Vf}$$

6.4.5 Measurement of Powder Compressibility

The compressibility Index and Hausner's Ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free flowing powder, such interactions are generally less and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the compressibility Index and the Hausner's Ratio Calculated by the formula

$$\text{Compressibility index: } = 100\frac{(V_0 - Vf)}{V_0}$$

$$\text{Hausner Ratio: } = \frac{V_0}{Vf}$$

6.5 Process Flow Chart of Direct compression

Fig no.6.1 Process Flow Chart of Direct compression:-

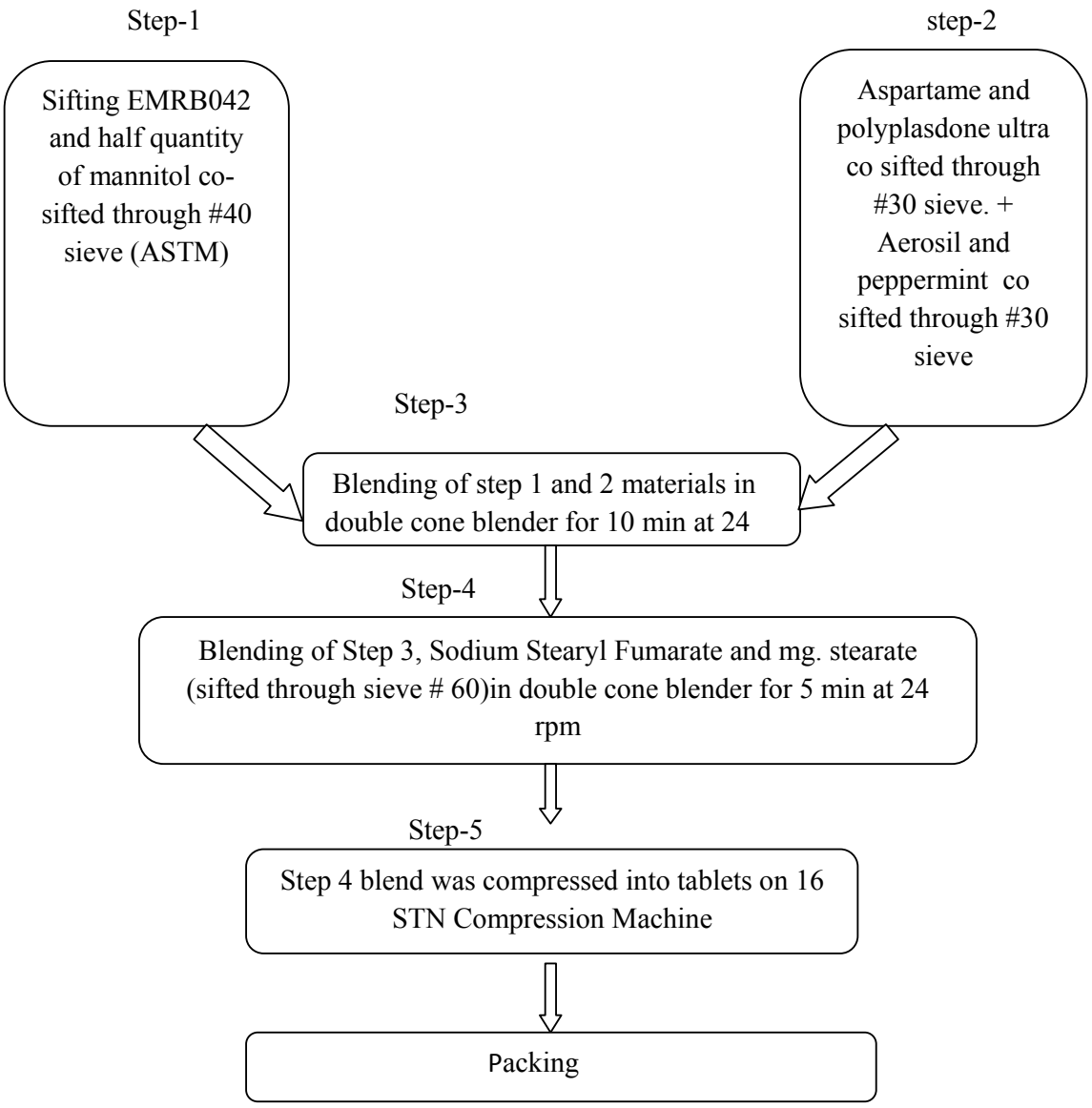


Table no.6.2 Formulation of Trial batches F1-F6

Sr. No.	Ingredients	Weight per Tablet (mg/tab)					
		F1	F2	F3	F4	F5	F6
1	EMRB042	14.53	14.53	14.53	14.53	14.53	14.53
2	MANNITOL	73.00	73.0	--	--	--	94.90
3	PROSOLVE HD	--	--	--	--	--	--
4	M.C.C.	41.87	43.87	--	--	--	20
5	CROSPOVIDONE	6.0	6.0	1.0	1.0	1.0	4.50
6	CROSPOVIDONE (Extra granular)	--	--	--	--	--	4.50
7	CROSCARMELLOSE SODIUM	6.0	6.0	--	--	--	2.0
8	AEROSIL	1	1	--	--	--	0.50
9	AEROSIL (Extra granular)						0.50
10	LUDIFLASH	--	--	119.72	119.72	119.72	115.8
11	CALCIUM SILICATE	--	---	---	---	---	---
12	IPA: WATER (ML)	--	---	---	---	---	Q.S
13	ASPARTAME	1.60	1.60	11.25	11.25	11.25	1.60
14	PEPPERMINT FLAVOR	0.0	0.0	2.0	2.0	2.0	0.50
15	TALC	--	--	--	--	--	--
16	SODIUM STEARYL FUMARATE	2.0	3.0	---	---	---	3.0
17	MAGNESIUM STEARATE	2.0	3.0	1.50	1.50	1.50	--
Total (mg)		150	150	150	150	150	150

Table no.6.3 Formulation of Trial batches F7-F13

Sr. No.	Ingredients	Weight per Tablet (mg/tab)						
		F7	F8	F9	F10	F11	F12	F13
1	EMRB042	14.53	14.53	14.53	14.86	14.86	14.86	14.86
2	MANNITOL	95.90	103.22	104.22	103.22	100.22	62.64	91.29
3	PROSOLVE HD	--	--	--	--	--	30	--
4	M.C.C.	20	--	--	--	--	--	--
5	CROSPOVIDONE	4.50	15	26.60	26.60	26.60	--	--
6	CROSPOVIDONE (Extra granular)	4.50	--	--	--	--	--	--
7	CROSCARMELLOSE SODIUM	2	--	--	--	--	--	--
8	AEROSIL	0.50	0.15	0.15	0.15	0.15	1	0.75
9	AEROSIL (Extra granular)	0.50	--	--	--	--	--	--
10	LUDIFLASH	--	115.82	--	--	--	--	--
11	CALCIUM SILICATE	--	--	--	--	--	7.50	7.50
12	IPA: WATER (ML)	q.s	--	--	--	--	--	--
13	ASPARTAME	1.60	1	1	1	1	2	2
14	PEPPERMINT FLAVOR	--	0.50	0.50	0.50	0.50	0.50	0.50
15	TALC	--	--	--	--	3.0	--	--
16	SODIUM STEARYL FUMARATE	2.50	3.0	3.0	4.0	4.0	6.0	6.5
17	MAGNESIUM STEARATE	2.50	--	--	--	--	--	--
18	POLY PLASDONE ULTRA	--	--	--	--	--	25.5	26.6
Total (mg)		150	150	150	150	150	150	150

6.6 Evaluation

6.6.1 Weight variation

Twenty tablets were randomly selected and weighed to determine the average weight

Limit	USP
10%	130mg or less
7.5%	130mg to 324mg
5%	More than 324mg

$$F = 100\left[\frac{W_0 - W}{W}\right]$$

F = Friability, W = Final weight, WO = Initial weight

6.6.4 Hardness Test

The hardness of tablet was carried out by using "Pharmg hardness tester" hardness tester.

6.6.5 Invitro Disintegration time

Keep six tablets in Disintegration apparatus. Note the time required for the all six tablets to disintegrate completely without leaving any residue on the mesh of apparatus. Mesh size kept 2mm (#10), stroke Cycles should be with rate of 28 to 32 cycles/min and 50 to 60 mm distance from bottom & top, control water temp $37^0C \pm 2^0C$. If 1 or 2 tablets fail, repeat for 12 tablets.

Limit for Orodispersible tablet

Within 1 min

6.6.6 Calculation for content uniformity

USP: - Active less than 25mg or 25%.

10 tablets limit NMT 1 tablet deviate 85 to 115% & none outside 75 to 125% of the Avg value/IP/BP/USP (Relative Standard Deviation less than or equal to 6%),

If 2 or 3 individual values are outside the limits 85 to 115% of the Avg value, & none outside 75 to 125% repeat for 20 tablets. Complies when 30 tablets NMT 3 of the individual values are outside the limit 85 to 115% of the Avg value, and none outside 75 to 125%.

6.6.7 Dissolution Study

Medium : 500 ml Phosphate buffer pH 6

Apparatus : Type II (paddle)

Speed : 50 rpm

Time : 5, 10, 15 min.

Temperature : $37^0C \pm 0.5\ ^0C$

λ max : 225nm

Perform the test on eight tablets place one tablet in each dissolution vessel containing 900 ml of water, at $37^0C \pm 0.5^0C$. At specified time withdrawn required amount of sample and take absorbance and calculate percentage release.

6.6.8 Calculation of similarity and dissimilarity factors

The similarity factor (f2) is a logarithmic transformation of the sum squared error of differences between the test T_t and reference products R_t over all time points. It represents closeness of two comparative formulations. Generally similarity factor in the range of 50 to 100 is acceptable according to US FDA. Among several methods investigated for dissolution profile comparison, f2 is the simplest. Moore and Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors, f1 and f2.Where Rt and Tt are the cumulative percentage dissolved at each of the selected n time points of the reference and test product respectively. The factor f1 is proportional to the average difference between the two profiles, where as factor f2 is inversely proportional to the average squared difference between the two profiles, with emphasis on the larger difference among all the time points. The factor f2 measures the closeness between the two profiles. Because of the nature of measurement, f1 was described as difference factor, and f2 as similarity factor. In dissolution profile comparisons, especially to assure similarity in product performance, regulatory interest is in knowing how similar the two curves are, and to have a measure which is more sensitive to large differences at any particular time point. For this reason, the f2 comparison has been the focus in Agency guidance

Calculation formulas

1) **Dissimilarity factor**

f1= $\{[\Sigma_{t=1}^{n} |R_t-T_t|] / [\Sigma_{t=1}^{n} R_t]\} \times 100$

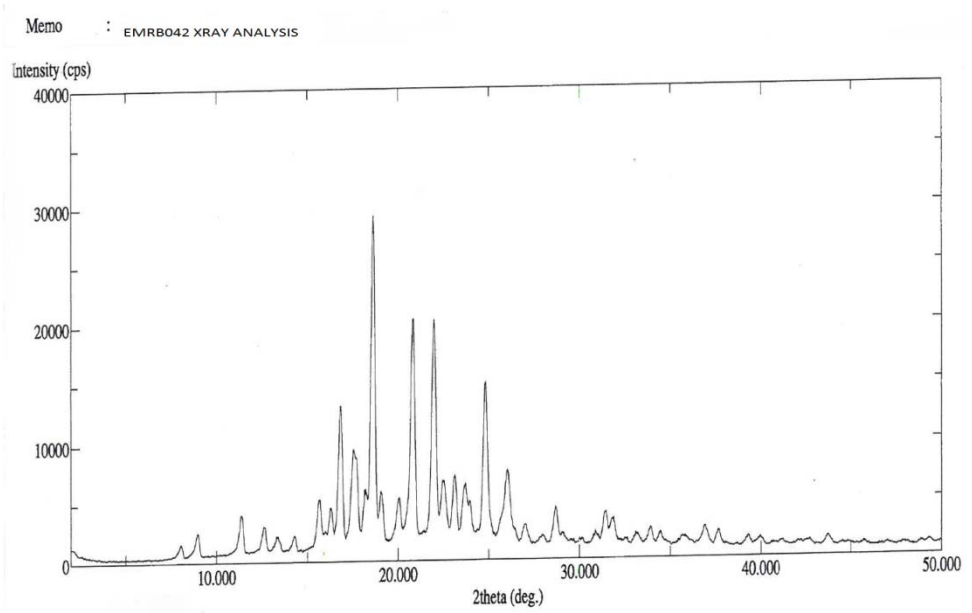
2) **Similarity factor**

f2= $50 \times \log \{[1+ (1/n) \Sigma_{t=1}^{n} (R_t-T_t)^2]^{-0.5} \times 100\}$

7 RESULTS AND DISCUSSION

7.1 Characterizations by X-ray diffraction method

Fig no-7.1 A.P.I characterization by X-ray diffraction method



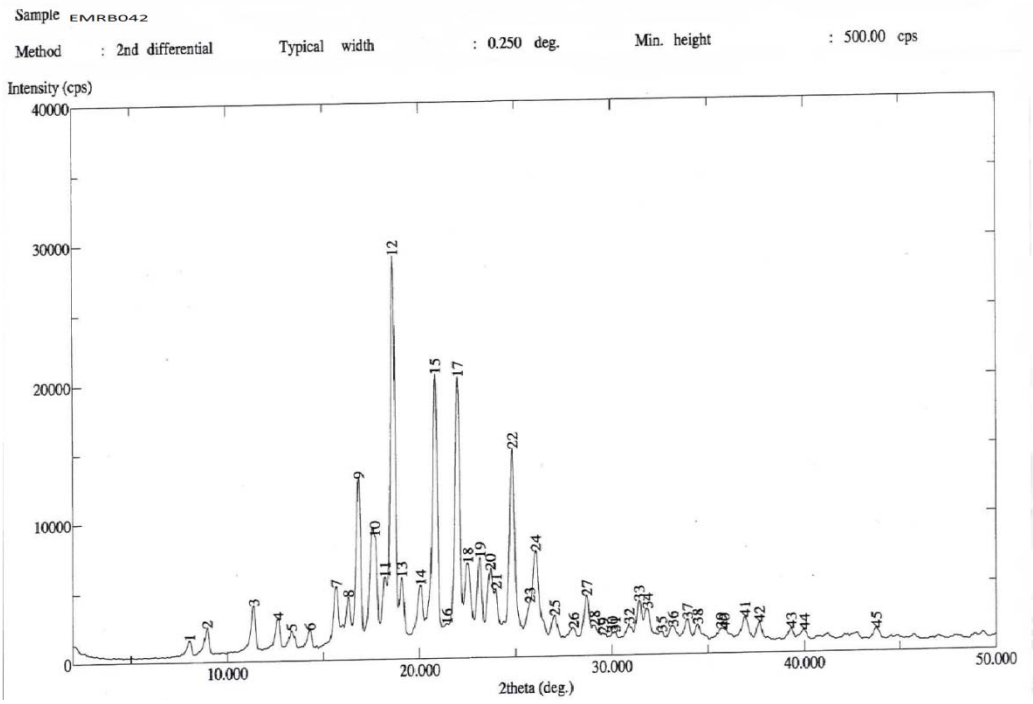


Table no.7.1 X.R.D Analysis of A.P.I

EMRB042		
Angle °2θ	d- spacing (A°)	Qualitative RI
18.6	4.76	100
20.8	4.26	71
22.0	4.03	70
24.8	3.58	52
16.8	5.26	46
17.7	5.01	31
26.0	3.41	27
23.1	3.84	25
22.5	3.94	24
23.7	3.75	22
19.1	4.64	21
18.2	4.87	21
15.7	5.65	19
20.1	4.42	19
23.9	3.70	18
16.3	5.43	16
28.7	3.10	16
11.4	7.76	15

X-ray diffraction technique employed for the analysis of the A.P.I. Readings obtained are compared with the patented A.P.I to confirm the identification and confirmation of the compound type. It was found to be type A compound. The results obtained were similar to that of the patented A.P.I. So A.P.I identified and confirmed.

7.2 Physicochemical parameters of the A.P.I.

7.2.1 Bulk density of the A.P.I

The bulk density of the A.P.I was within the range of 0.425gm/ml to 0.477gm/ml.

7.2.2 Taped density of the A.P.I

The taped density of the A.P.I was within the range of 0.502 gm/ml to 0.565gm/ml.

7.2.3 Compressibility index of the A.P.I

The compressibility index was in the range of 14.28 to 16.13.

7.2.4 Hausner's ratio of the A.P.I

The Hausner's ratio was in the range of1.16 to1.24 So as the reading indicates the A.P.I was having very poor flow rate

7.2.5 Particle size of the A.P.I by Malvern Mastersizer 2000

Fig no.7.2 Particle size analysis of A.P.I by Malvern Mastersizer 2000

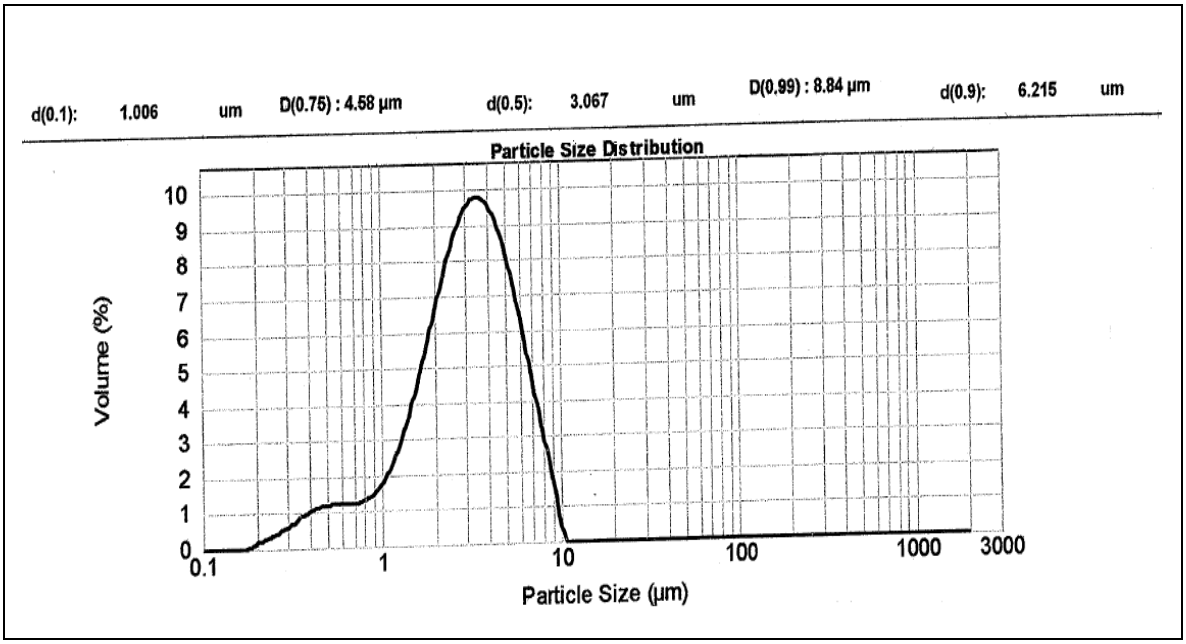


Table no. 7.2 Particle size analysis of A.P.I by Malvern Mastersizer 2000

Size(µm)	Vol under %	Size(µm)	Vol under %	Size(µm)	Vol under %
1.00	9.83	40.00	100.00	750.00	100.00
1.445	16.10	50.00	100.00	800.00	100.00
2.oo	26.87	60.00	100.00	900.00	100.00
2.512	38.12	70.00	100.00	1000.0	100.00
3.832	63.68	100.00	100.00	1500.0	100.00
4.366	72.73	150.00	100.00	2000.0	100.00
5.00	79.94	200.00	100.00	2500.00	100.00
6.607	92.22	250.00	100.00	3000.00	100.00
7.586	96.19	300.00	100.00	3500.00	100.00
8.710	98.78	350.00	100.00	4000.00	100.00
10.00	100.00	400.00	100.00	4500.00	100.00
13.183	100.00	450.00	100.00	5000.00	100.00
14.00	100.00	500.00	100.00		
15.00	100.00	550.00	100.00		
20.00	100.00	600.00	100.00		
25.00	100.00	650.00	100.00		
30.00	100.00	700.00	100.00		

D (0.5) value with the A.P.I was found to be 3.063, so A.P.I was found to be of desired particle size.

7.3 Compatibility Study by D.S.C technology and HPLC technology

7.3.1 H.P.L.C technology

Table no 7.3 A.P.I-Excipients compatibility studies by HPLC technology

Sample name	Impurity				
		Initial	40°C/75% RH 1 M open	40°C/75% RH 1M closed	55°C 1 M open
EMRB042 Benzoate	Dimer impurity	0.039	0.065	0.056	0.039
	Unknown	0.034	0.032	0.035	0.033
	Total	0.214	0.254	0.275	0.234
EMRB042 benzoate +	Dimer impurity	0.040	0.038	0.035	0.035

Mannitol	Unknown	0.036	0.035	0.037	0.036
	Total	0.236	0.236	0.249	0.232
EMRB042 + Colloidal silicon dioxide	Dimer impurity	0.023	0.000	0.025	0.000
	Unknown	0.122	0.033	0.125	0.127
	Total	0.360	0.190	0.401	0.351
EMRB042 + Crospovidone	Dimer impurity	0.044	0.052	0.029	0.028
	Unknown	0.129	0.388	0.631	0.677
	Total	0.349	0.676	0.859	0.880
EMRB042 + Croscarmellose sodium	Dimer impurity	0.000	0.000	0.000	0.000
	Unknown	0.030	0.029	0.035	0.036
	Total	0.162	0.178	0.195	0.166
EMRB042 + Aspartame	Dimmer impurity	0.032	0.035	0.034	0.030
	Unknown	0.034	0.035	0.036	0.036
	Total	0.199	0.236	0.258	0.227
EMRB042 + Peppermint flavor	Dimer impurity	0.032	0.030	0.029	0.027
	Unknown	0.032	0.036	0.043	0.048
	Total	0.232	0.242	0.264	0.261
EMRB042 + Sodium stearyl Fumarate	Dimer impurity	0.016	0.018	0.015	0.019
	Single unknown	0.032	0.032	0.035	0.029
	Total	0.211	0.214	0.238	0.208
EMRB042 +	Dimer	0.034	0.033	0.028	0.035

Ludiflash	impurity				
	Single unknown	0.034	0.034	0.036	0.037
	Total	0.232	0.262	0.255	0.223
EMRB042 + Prosolve ODT	Dimer impurity	0.000	0.000	0.000	0.000
	Single unknown	0.031	0.031	0.031	0.030
	Total	0.189	0.194	0.199	0.189

All Excipients found to be compatible.

7.3.2 Compatibility study by D.S.C method

7.3.1 The thermo gram obtained by the D.S.C technology with pure A.P.I

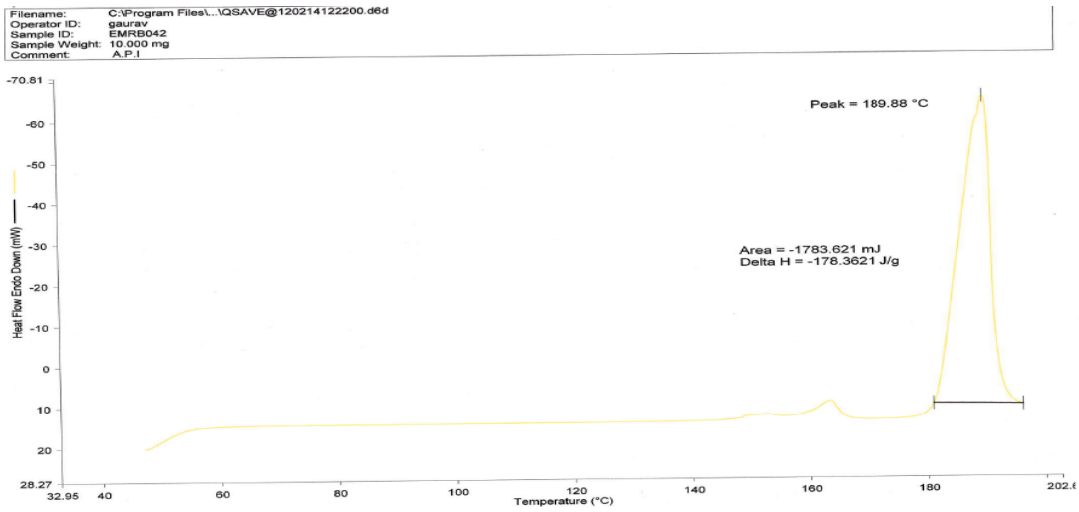


Fig no.7.3 Thermo gram obtained by the D.S.C technology with pure A.P.I

The thermo gram obtained with A.P.I shows pick at 180.88.

7.3.2 The thermo gram obtained by the D.S.C technology with pure A.P.I and mannitol:

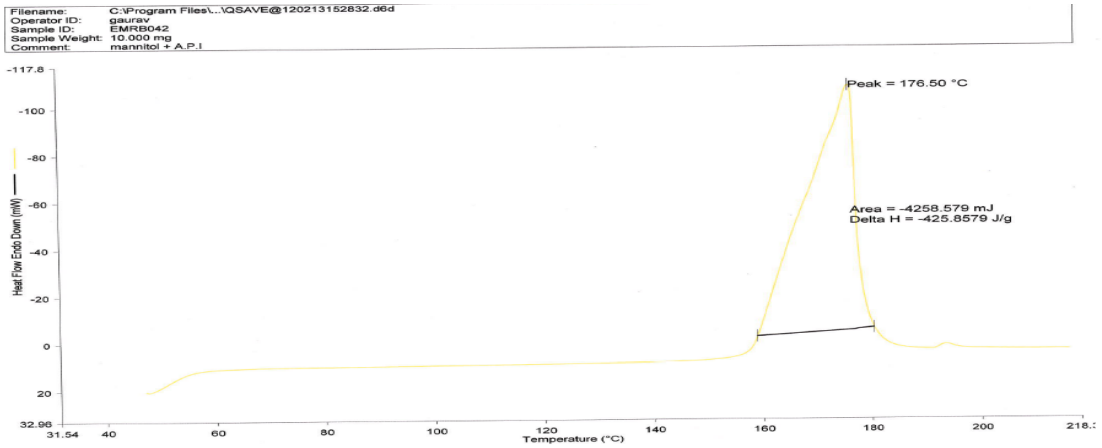


Fig no.7.4 The thermo gram obtained by the D.S.C technology with pure A.P.I and mannitol

No significant change is observed in melting point.

7.3.4 The thermo gram obtained by the D.S.C technology with pure A.P.I and polyplasdone XL:-

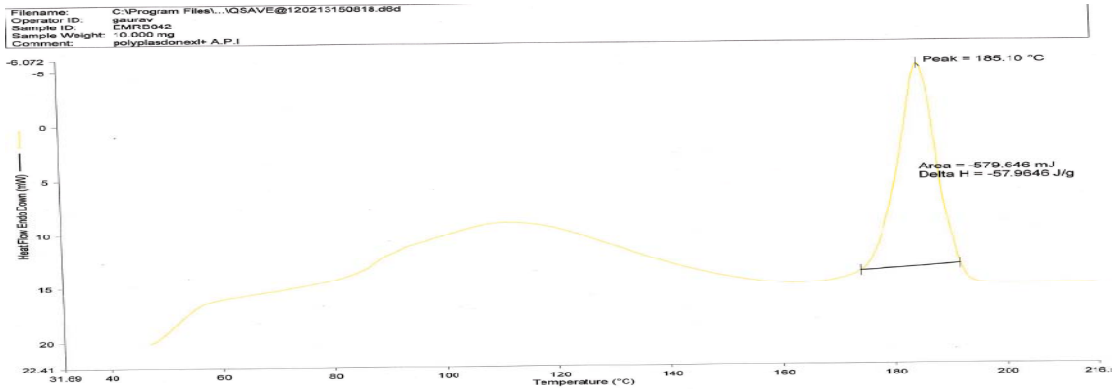


Fig no.7.5 Thermo gram obtained by D.S.C technology with pure A.P.I and polyplasdone XL

No significant change in the melting point is observed

7.3.4 The thermo gram obtained by the D.S.C technology with pure A.P.I and peppermint flavor

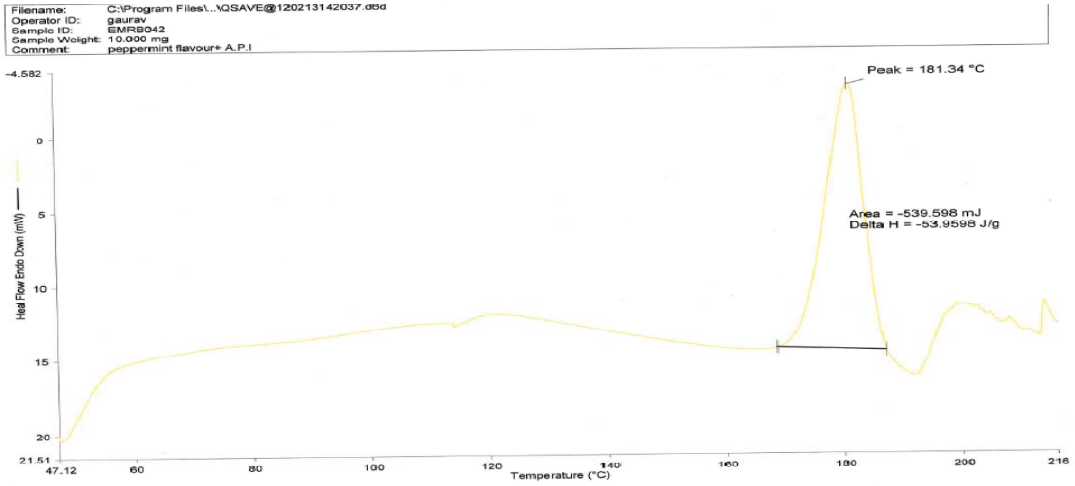


Fig no.7.6 Thermo gram obtained by D.S.C technology with pure A.P.I and peppermint flavor

No significant change in the melting point is observed

7.3.5 The thermo gram obtained by the D.S.C technology with pure A.P.I and Aspartame

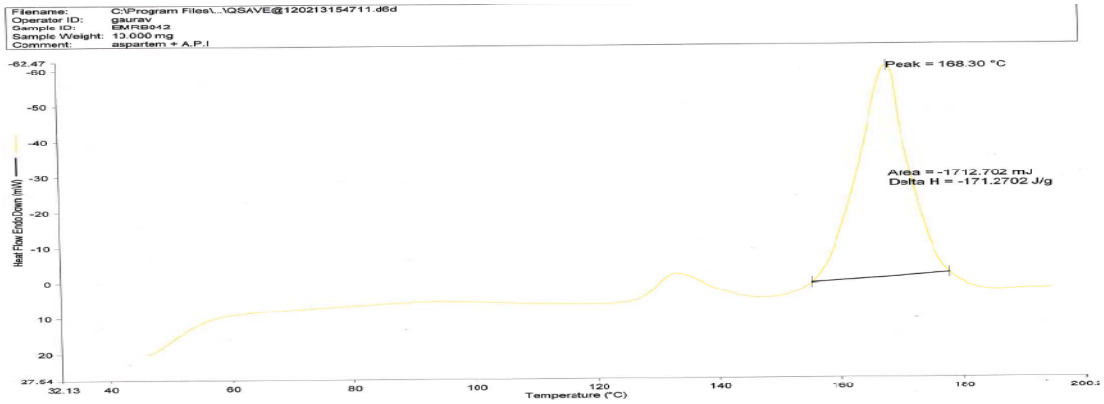


Fig no 7.7 The thermo gram obtained by the D.S.C technology with pure A.P.I and Aspartame

No significant change in the melting point .All excipients were found to be compatible with the A.P.I

7.4 Evaluation of powder blend

The prepared granules were evaluated for the blend property like Bulk density, Tapped density, Carr's index, Hauser ratio and Angle of repose. Results obtained were as shown in Table 8.3 below- (n = 3)

Table no. 7.4 Evaluation of powder blend

Formulations	Bulk density(g/ml) ±SD	Tapped density (g/ml) ±SD	Carr's index (%)±SD	Hausner ratio (%)±SD
F1	0.444	0.526	15.55	1.18
F2	0.476	0.571	16.66	1.20
F3	0.476	0.565	14.28	1.16
F4	0.425	0.502	14.89	1.17
F5	0.430	0.507	15.04	1.18
F6	0.462	0.544	16.13	1.26
F7	0.456	0.536	15.89	1.24
F8	0.439	0.516	15.29	1.19
F9	0.477	0.560	16.59	1.29
F10	0.434	0.509	15.07	1.17
F11	0.445	0.521	15.42	1.19

The above result showed that, the Carr's index in the range of 10-20% which is considered as excellent to good flowing property. Similarly, the bulk density and tapped density value was found to be less than one hence showed excellent to good flow property. All these results indicate that, the powder blend possess satisfactory flow and compressibility properties for directly compressible formulation.

7.5 Physical evaluation of tablets

All the tablet preparations were evaluated for various physical parameters and assay before proceeding further. Following table includes the values (mean ± SD) of weight variation, hardness, diameter and thickness of 11 tablet batches prepared using different combinations of functional excipients.

Table no.7.5 Evaluation of tablets

Formulation	Hardness (Kp)	Weight Uniformity(mean) (mg)	Friability (%)	Thickness (mm)
F1	3.01 – 4.23	149	0.067	3.31 - 3.32
F2	3.01 – 4.23	149	0.067	3.31 - 3.32
F3	2.74-3.50	150.8	0.301	3.24-3.26
F4	2.35 – 3.30	149.7	0.215	3.48 – 3.53
F5	2.35 – 3.30	149.7	0.215	3.48 – 3.53
F6	3.25 – 4.07	149.8	0.121	3.52 – 3.54
F7	3.80– 5.28	151.2	0.106	3.56 – 3.59
F8	2.01-2.92	149.5	0.045	3.26-3.33
F9	3.88 -4.43	150.1	0.076	3.50 - 3.53
F10	4.7-5.6	151.1	--	3.64-3.66
F11	5.4-8.01	150.3	--	3.58-3.66

The percentage friability, as depicted in table was in the range 0.06 to 0.2**.** Tablet weight in all the eight batches varied in range of 149.0 to 151.0. Thickness was in the range of 3.24 mm to 3.64 mm and tablet hardness between 2.01 to 5.4. Thus, all the physical parameters of the compressed tablets were within control.

7.5.1 In vitro Disintegration time

The disintegration study was carried on all formulations except formulation no.1 and formulation no.6 as sticking was observed, the disintegration study of remaining formulations are as follows.

Table no 7.6 Values of Disintegration time orodispersible

Formulation	Disintegration Time(Sec)
F2	20 sec
F3	20 sec
F4	19 Sec
F5	14 Sec
F7	14 Sec
F8	22 sec
F9	24 sec
F10	24 se
F11	24 sec
F12	16 sec
F13	12 sec

It was observed that tablets of all the eleven formulations had a disintegration time of less than 30 sec. and hence they passed the test for disintegration time. It was seen that formulation batches 4, 5, 10, 11, had a disintegration time less than 20 sec. i.e. the disintegration time was found to decrease. However, at higher concentrations of Croscarmellose sodium and calcium silicate i.e about 4 to 5 % of either of them drastically decreases the disintegration time.

7.5.2 Uniformity of Content

The drug content for tablets of all formulation was found to be in the range of. -101.3±1.33 thus all formulation batches of EMRB042 passes the content uniformity test.

7.5.3 In vitro Dissolution Studies

The dissolution study was carried on all formulations except formulation no. 1 and formulation no.6 as sticking was observed, the dissolution study of remaining formulations are as follows.

FORMULATION 2

Percentage release of EMRB042 in water of optimum formulations prepared by employing direct compression technique

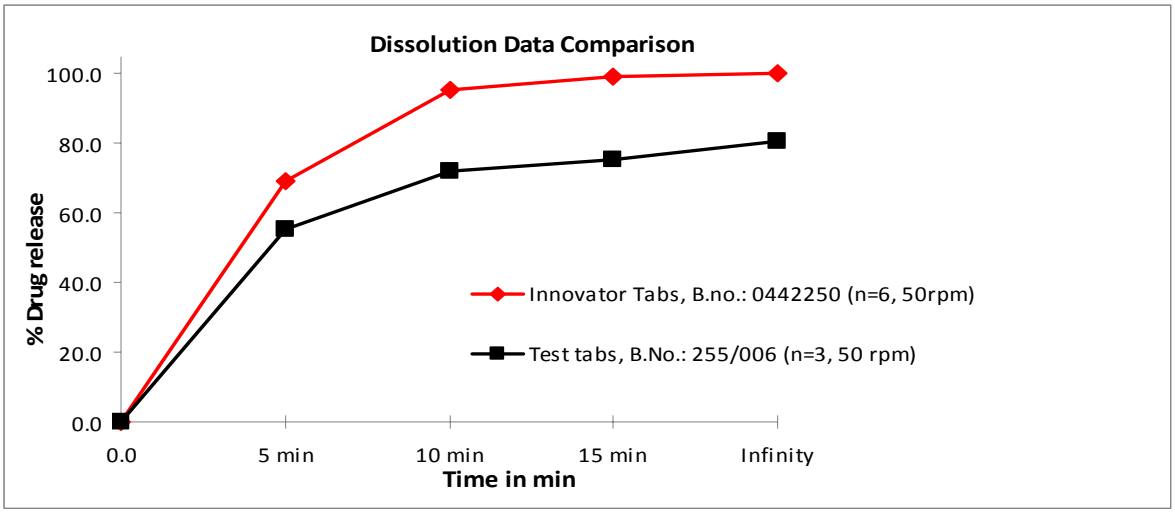


Fig no. 7.8 Percentage release of F2

Table no.7.7 Dissolution profile of F2

Time points	% DRUG RELEASE				
	5 min	10 min	15 min	Infinity	F2
Reference	69.4	95.6	99.2	100.4	
Test Product	55.6	71.9	75.2	80.5	39.0

The % release after infinity period of 30 min with 200rpm was not complete with formulation no. 2.As the release was not complete, it was decided to use ludiflash for direct compression method.

FORMULATION 3

Percentage release of EMRB042 in water of optimum formulations prepared by employing direct compression technique with ludiflash

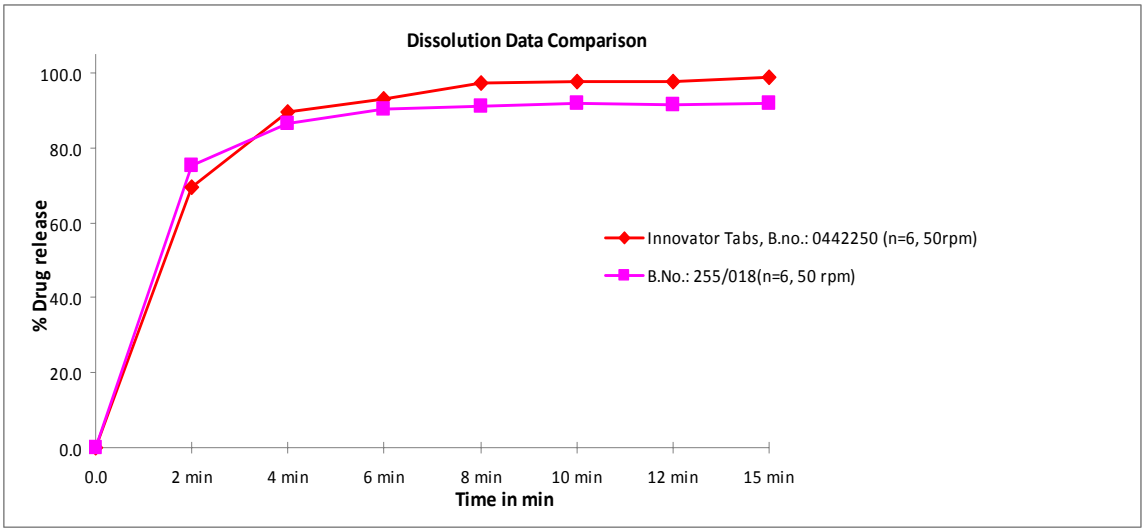


Fig no.7.9 Percentage release of F 3

Table no.7.78 Dissolution profile of F 3

Time points	% DRUG RELEASE							
	2Min	4Min	6Min	8Min	10Min	12Min	15Min	F2
Innovator	69.5	89.7	93.1	97.5	97.8	97.5	98.7	
Formulation No.3	75.2	86.5	90.4	91.0	91.8	91.4	91.9	64.0

After period of 15 min. with 50rpm % release was on higher side compared to formulation no. 2. It was decided to further investigate the effect of particle size reduction of EMRB042 on dissolution profile. So two batches were designed with milled EMRB042 and micronized EMRB042

Formulation 4 & 5

Percentage release of EMRB042 in water of formulations prepared by employing direct compression technique

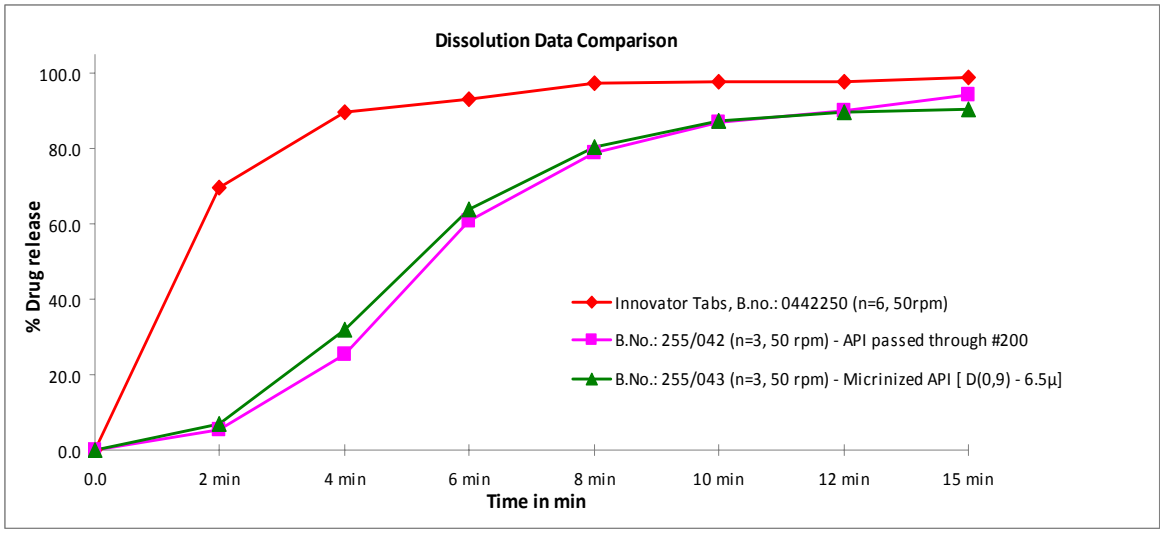


Fig no 7.10 Percentage release of F 4 & 5

Table no.7.9 Dissolution profile of F4 & F5

Time points	% DRUG RELEASE							
	2 min	4min	6min	8min	10min	12min	15 min	F2
API milled F4	5.2	25.5	60.9	78.9	87.0	89.9	94.1	52
APImicronized-F5	7.1	32.0	63.7	80.3	87.1	89.7	90.4	47

After 15 min the % release of drug observed was better in milled EMRB042 (200 mesh passed) than micronized EMRB042. As the release pattern was better in formulation containing milled EMRB042, so it was decided to use milled EMRB042, but % release was not complete so it was decided to use wet granulation technique.

FORMULATION 7

Percentage release of EMRB042 in water of optimum formulations prepared by employing wet granulation technique

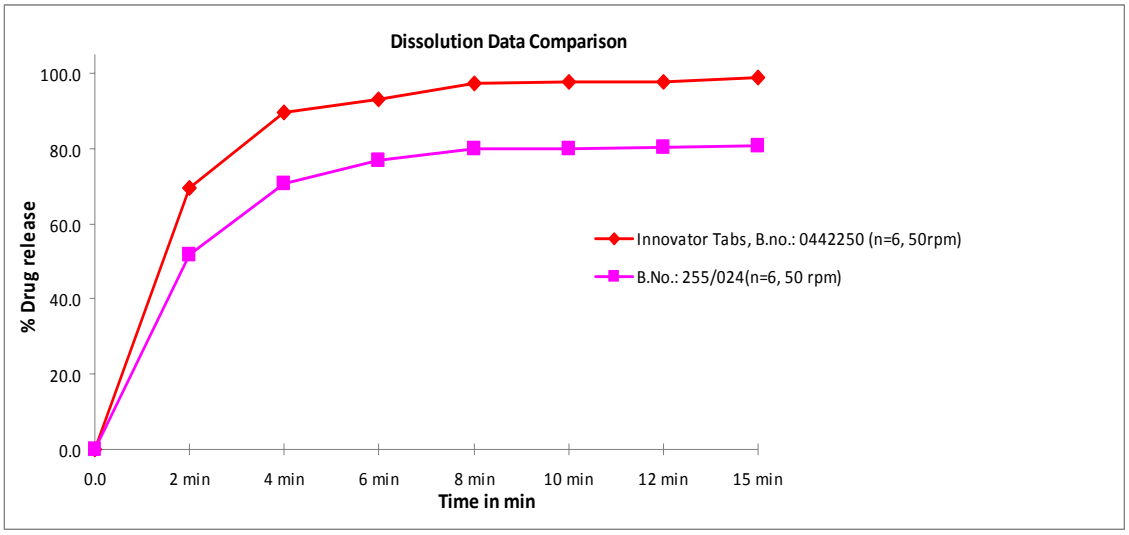


Fig no.7.11 Percentage release of F 7

Table no.7.10 Dissolution profile of F 7

Time points	% DRUG RELEASE							
	2 min	4 min	6 min	8 min	10 min	12 min	15 min	F2
Reference	69.5	89.7	93.1	97.5	97.8	97.5	98.7	-
Formulation 7	51.9	70.7	76.9	79.8	79.9	80.4	80.6	39.0

After 15 min the % release observed was not complete. As the dissolution profile obtained with the approach of wet granulation was not 100 % after 15 min it was decided to stick with the approach of direct compression formulation with ludiflash and reduce the concentration of peppermint and to use sodium Stearyl Fumarate instead of mg. stearate.

FORMULATION 8

Percentage release of EMRB042 in water of optimum formulations prepared by employing direct compression technique with reduced concentration of peppermint and use of sodium Stearyl Fumarate instead of mg. stearate

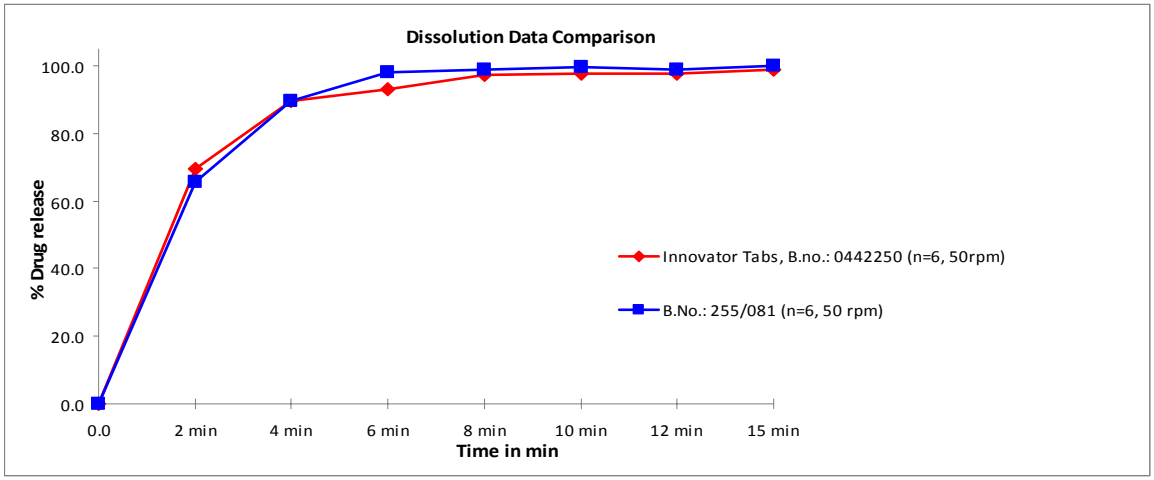


Fig no.7.12 Percentage release of F 8

Table no.7.11 Dissolution profile of F8

Time points	% DRUG RELEASE							
	2 min	4 min	6 min	8 min	10 min	12 min	15 min	F2
Innovator	69.5	89.7	93.1	97.5	97.8	97.5	98.7	-
Formulation 8	65.5	89.7	98.1	99.0	99.5	98.8	100.1	79.0

The % release after time period of 15 min observed was better than the innovator. The % release after time period of 15 min Observed was better than innovator so it was decided to kip sodium Stearyl Fumarate as the only lubricant in the formulation. The formulation was kept for the stability in 40°C temperature with 75% Relative humidity.

Table no.7.12 Test product (Ludiflash formula) - stability data of F8

EMRB 042 ODT						
Pack Details: HDPE Bottle						
Sr. No.	Test	Specifications	Initial Analysis	55°C (Open)	40°C/75%RH	
				15Days	15 days	15 days
1	Dissolution (%)	Time Points				
	0.1N HCl ,500 ml, USP Type II 50 rpm	5 min	Na	11.3	26.7	12.5
		10 min	91.4	16.5	47.6	32.4
		15 min	89.8	27.9	70.6	50.5
		30 min	Na	54.9	84.3	Na
2	Water Content (%)	To establish	2.99	NP	NP	NP
3	Assay (%)	90.0 – 110.0	97.89	97.02	97.83	97.36
	Related Substances (%)	Tentative limits				
	Dimer	0.5%	ND	ND	ND	ND
4	Unknown	0.2%	0.103	0.808	0.586	0.584
	Total Impurities	2.0%	0.180	0.964	0.700	0.687

Though assay after 15 days was within the limits, the range of single unknown impurity observed was 0.687 which is not acceptable. Formulation was not stable over 15 days in stability conditions of 40°C Temperature and 75% relative humidity. It was decided to remove ludiflash from formulation as ludiflash contains crosspovidone which carries traces of organic solvents with it & may cause oxidation of the EMRB042.Resulting rise in unknown impurity. Mannitol was decided to be used as filler because of its high Solubility of 42gms/ml.

FORMULATION 9

Percentage release of EMRB042 in water of optimum formulations prepared by employing direct compression technique with mannitol as filler

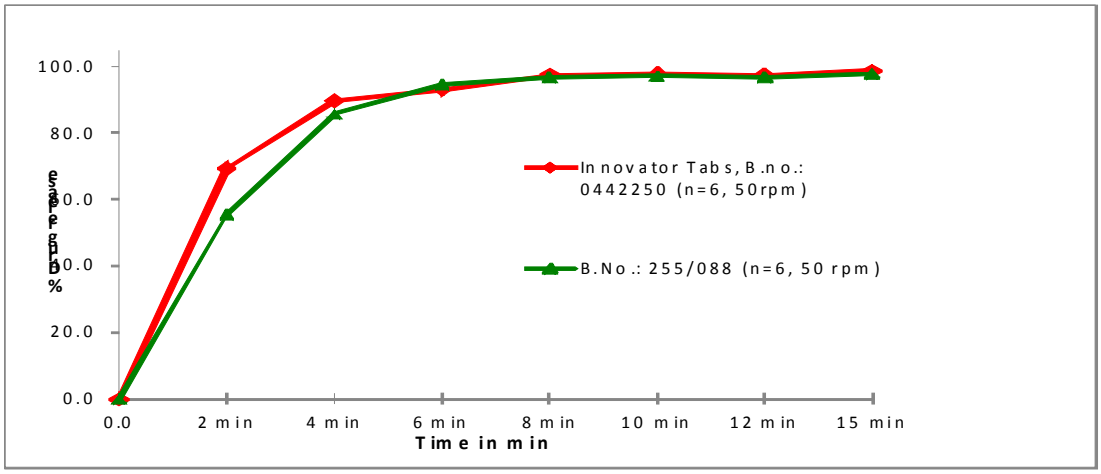


Fig no.7.13 Percentage release of F 9

Table no:-7.13 Dissolution profile of F9

Time points	% DRUG RELEASE							
	2 min	4 min	6 min	8 min	10 min	12 min	15 min	F2
Innovator	69.5	89.7	93.1	97.5	97.8	97.5	98.7	-
Formulation 9	55.5	85.7	94.6	96.7	97.1	96.8	97.8	64.0

Dissolution profile obtained was better than the innovator with formulation with mannitol as filler. As the profile obtained was satisfactory it was decided to further investigate the role of mannitol with different grades. Mannitol SD 200 & Mannitol 300 DC were selected as a requirement of formulation for better solubility, Stability and release profile.

FORMULATION NO:-10 & 11

Percentage release of EMRB042 in water of optimum formulations prepared by employing direct compression technique

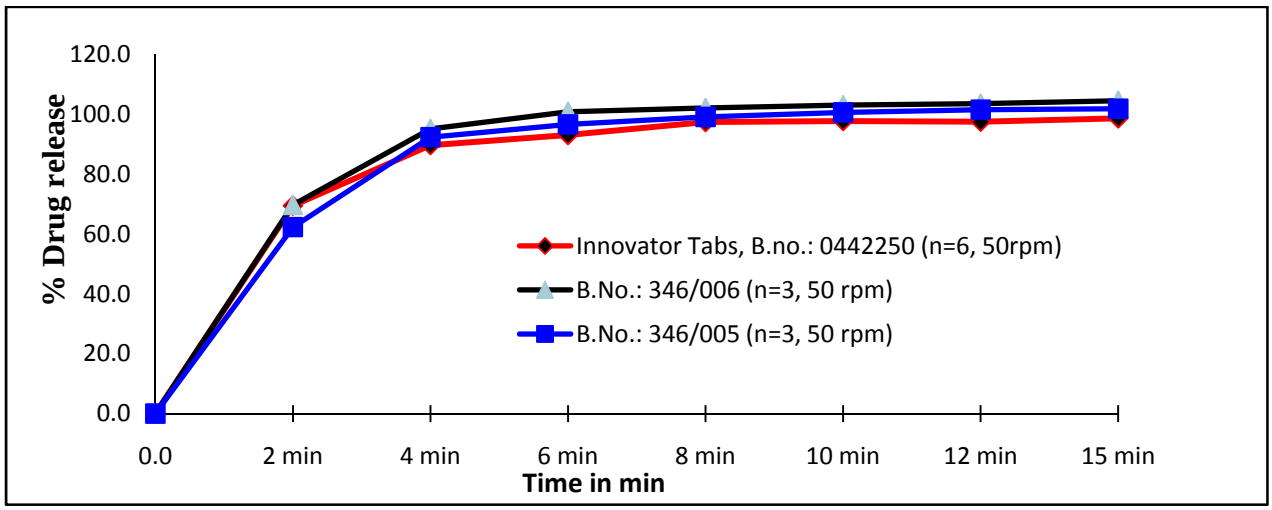


Fig no.7.14 Percentage release of F10 & F11

Table no:-7.14 dissolution profile of F10 & F11

Time points	% DRUG RELEASE							
	2 min	4 min	6 min	8 min	10 min	12 min	15 min	F2
Reference	69.5	89.7	93.1	97.5	97.8	97.5	98.7	-
annitol 300DC F10	69.7	95.1	100.9	102.2	103.1	103.6	104.6	64
Mannitol SD200 F11	62.3	92.4	96.7	99.2	100.7	101.6	101.9	71

Dissolution profile obtained was better than the reference in both mannitol grade formulations specifically mannitol with grade 300DC has shown better results as compare to SD 200. As the results obtained with both mannitol grades are better than the reference, F10 kept for stability study in 40°C Temperature and 75% Relative humidity.

Table no:-7.15 Test product Stability data of F10

EMRB 042 ODT						
Sr. No.	Test	Specifications	Initial Analysis	55°C (Open)	40°C/75%RH	
				15Days	15 days	15 days
1	Dissolution (%	Time Points				
	Deaerated water ,900 ml, USP Type II 50 rpm	5 min	Na	78.8	76.9	39.4
		10 min	97.1	93.2	95.0	70.8
		15 min	97.8	94.9	97.0	83.7
		30 min	Na	96.2	96.4	90.3
2	Water Content (%)	To be established	3.86	3.57	3.49	3.77
3	Assay (%)	90.0 – 110.0	97.18	97.18	97.60	97.53
4	Related Substances (%)	Tentative limits				
	Dimer	0.2%	ND	ND	ND	ND
	Unknown	0.2%	0.192	1.744	0.610	1.115
	Total Impurities	2.0%	0.328	1.917	0.739	1.249

Even though % release obtained with F10 was complete after 15 days, stability issue continued with the formulation. As the single unknown impurity observed was 1.249 which is not acceptable.As the stability issue continued even with the mannitol formulation it was decided to use prosolve HD (silicified microcrystalline cellulose), polyplasdone ultra (cross povidone) & hubersorb 250 (Calcium silicate)

FORMULATION NO -12 &13

Percentage release of EMRB042 in water of optimum formulations prepared by employing direct compression technique

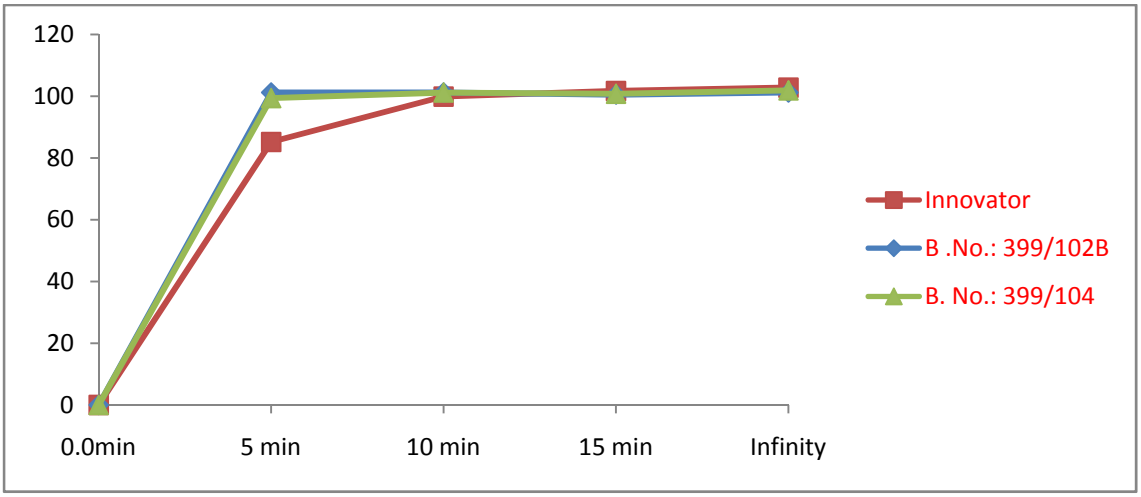


Fig no. 7.15 Percentage release of F 12 & F13

Table no .7.16 Dissolution profile of F12 & F13

Time points	% DRUG RELEASE				F2
	5 min	10 min	15 min	Infinity	
Reference	85.2	99.9	101.7	102.8	
F12	101.2	101.2	100.5	101.2	56
F13	99.4	101.2	100.8	101.9	54

Percent release obtained with the prosolve HD (silicified microcrystalline cellulose), polyplasdone ultra (cross povidone) & hubersorb 250 (Calcium silicate), was complete as well as better than reference sample. Dissolution profile obtained from this formulation was fond to be satisfied so it was decided to keep it for stability in 40^0C temperature and 75% relative humidity.

Table no. 7.17 Test product stability data of F12

EMRB 042 ODT						
Sr. No.	Test	Specifications	Initial Analysis	40°C/75%RH		
				15 days	1month	2month
1	Dissolution (%	Time Points				
	Deaerated water ,900 ml, USP Type II 50 rpm	5 min	101.2	Na	na	Na
		10 min	101.2	97.3	90.6	89.0
		15 min	100.5	97.3	97.3	98.4
		30 min	101.2	Na	na	Na
2	Water Content (%)		4.46	4.26	NP	3.74
3	Assay (%)	90.0 – 110.0	100.81	98.66	100.04	96.28
4	Related Substances (%)	Tentative limits				
	N-oxide	0.2%	0.034	0.046	0.046	0.068
	Unknown	0.2%	0.049	0.044	0.044	0.050
	Total Impurities	2.0%	0.139	0.133	0.150	0.162

The total impurity at the end of two months was 0.162 with F12 which is acceptable limit.

Table no 7.18 Test product stability data of F13

EMRB 042 ODT						
Sr. No.	Test	Specifications	Initial Analysis	40°C/75%RH		
				15 days	1month	2month
1	Dissolution (%	Time Points				
	Deaerated water ,900 ml, USP Type II 50 rpm	5 min	97.3	na	na	Na
		10 min	99.5	96.2	95	66
		15 min	99.6	96.3	95.4	92.1
		30 min	99.6	na	na	Na
2	Water Content (%)		3.78	3.40	3.84	3.09
3	Assay (%)	90.0 – 110.0	101.48	101.75	100.12	101.28
4	Related Substances (%)	Tentative limits				
	N-oxide	0.2%	0.027	0.038	0.05	0.075
	Unknown	0.2%	0.052	0.048	0.048	0.053
	Total Impurities	2.0%	0.141	0.129	0.164	0.179

The total impurity at the end of two months with F13 was 0.179 which is in an acceptable limit.

8 SUMMARY

EMRB042 is an anti-migraine drug used to control the acute migraine attacks with or without aura. It is well absorbed from the gastrointestinal tract. However, the faster release of the drug was expected for faster relief in the acute attacks of the migraine. So there is strong need to enhance the disintegration & dissolution rate of the formulation. The half life of the drug is 2to 3 hrs. Therefore, it is suitable drug for design of fast dissolving tablets with a view to improve its oral bioavailability.

In present study, an attempt was made to design ODTs of EMRB042 using super disintegrant like croscarmellose sodium, Crospovidone, microcrystalline cellulose to decrease the disintegration time of tablets and also to increase drug bioavailability.

Characterization of the A.P.I was done by XRD, which confirmed the A.P.I is crystal form I.

Selections of excipients were done as per the requirement of the formulation. As aim was to formulate the ODT formulation, most simple technology of direct compression was followed. Basic categories of excipients like filler, super disintegrant, binder, sweetener, lubricant, glident ware identified and accordingly excipients were selected. As the A.P.I is sensitive to oxidation, excipients were selected containing low peroxide content to prevent the oxidation. Selected excipients we subjected to compatibility study.

In compatibility study A.P.I was kept with all the excipients in 1:1 proportion to study the possible interaction. Drug and excipients were subjected to three different conditions of temperature and relative humidity, 40^0 C/75% RH open, 40^0C/75%RH closed, 55^0C closed for the period of 1 month and then samples were evaluated for the compatibility using HPLC technology and D.S.C technology. HPLC and DSC study suggested there is no interaction between the drug and excipients.

Formulations were prepared by direct compression method and evaluated, for the parameters such as weight variation, content uniformity, friability, hardness, disintegration time, dissolution profile, assay, and stability.

Formulation 1 showed sticking on both the punch surface so it was decided to increase the concentration of the magnesium stearate, sodium Stearyl Fumarate up to 2%.

Formulation 2 with reduced concentration of the lubricant showed incomplete release of the A.P.I of 75% at the end of the 15min where as reference sample showed 100%. So it was

decided to use ludiflash as filler which is the combination of three excipients mannitol, crospovidone, and polyvinyl acetate.

Formulation 3 with ludiflash as filler showed % release of 94%.

To study the effect of particle size on dissolution profile of the drug milled A.P.I and micronized A.P.I used in formulation 5 & formulation 6 respectively both the formulations showed release of 94% and 90% respectively after 15min. So it was decided to keep formulation 5 for stability.

Evaluation of formulation 5 on the 15^{th} day showed unknown impurity above the limit.

Formulation 6 designed with the approach of wet granulation which showed sticking on both punches.

Formulation 7 designed with wet granulation and increased concentration of 1.7 % so no sticking was observed. The % release was 80% so it was decided to stick with direct compression method.

Formulation 8 was designed with reduced concentration of peppermint flavor and sodium stearyl fumarate instead of magnesium stearate. Percentage release was 100 %. So formulation 8 was kept for stability but impurity level crossed acceptable limit over the period of 15 days. So it was decided to use mannitol as filler.

Formulation 9 with mannitol showed release of 98.8% of release. So to study the effect of the mannitol particle size two grads of mannitol were selected.

Formulation 10 with pearlitol 300DC and formulation 11 with pearlitol SD200 were designed both the formulations showed complete release but formulation 10 showed better release profile. So it was kept for stability. But impurity level crossed the acceptable limit within 15days.so it was decided to add prosolve HD, polyplasdone ultra & Calcium silicate.

Formulation 12 designed with prosolve, polyplasdone ultra & Calcium silicate showed 100% release were as formuletion 13 with increased level of showed polyplasdone ultra showed 100% release. both of these formulations were found to be stable over the period of 2 months. So both the formulations ware selected as the final optimized formulations.